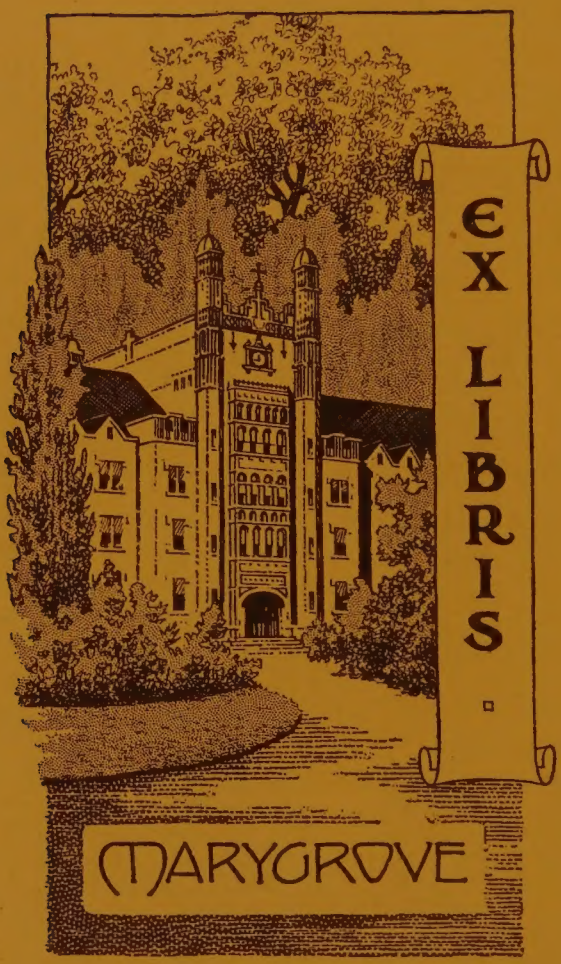
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MOLECULAR REARRANGEMENTS

BY

C. W. PORTER

PROFESSOR OF CHEMISTRY IN THE
UNIVERSITY OF CALIFORNIA

American Chemical Society
Monograph Series

BOOK DEPARTMENT

The CHEMICAL CATALOG COMPANY, *Inc.*

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GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, Secretary of the American Chemical Society, Washington, D. C.; John E. Teeple, Treasurer of the American Chemical Society, New York City; and Professor Gellert Alleman of Swarthmore College. The Trustees have arranged for the publication of the American Chemical Society series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company of New York City.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed the editors, named at the close of this introduction, to have charge of securing authors, and of considering critically the manuscripts prepared. The editors of each series will endeavor to select topics which are of current interest and authors who are recognized as authorities in their respective fields. The list of monographs thus far secured appears in the publisher's own announcement elsewhere in this volume.

The development of knowledge in all branches of science, and especially in chemistry, has been so rapid during the last fifty years and the fields covered by this development have been so varied that it is difficult for any individual to keep in touch with the progress in branches of science outside his own specialty. In spite of the facilities for the examination of the literature given by Chemical Abstracts and such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie and the English and French Dictionaries of Chemistry, it often takes a great deal of time to coördinate the knowledge available upon a single topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value to their fellow chemists.

It was with a clear recognition of the usefulness of reviews of this character that a Committee of the American Chemical Society recommended the publication of the two series of monographs under the auspices of the Society.

Two rather distinct purposes are to be served by these monographs. The first purpose, whose fulfilment will probably render to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a readable form, intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs will enable such men to form closer contact with the work of chemists in other lines of research. The second purpose is to promote research in the branch of science covered by the monograph, by furnishing a well digested survey of the progress already made in that field and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, it is intended to include extended references to the literature, which will enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection will be made of those papers which are most important.

The publication of these books marks a distinct departure in the policy of the American Chemical Society inasmuch as it is a serious attempt to found an American chemical literature without primary regard to commercial considerations. The success of the venture will depend in large part upon the measure of coöperation which can be secured in the preparation of books dealing adequately with topics of general interest; it is earnestly hoped, therefore, that every member of the various organizations in the chemical and allied industries will recognize the importance of the enterprise and take sufficient interest to justify it.

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Preface

A rearrangement may be defined as a unimolecular reaction which results in a structural modification of the molecule. As a rule the product formed is isomeric with the original compound but this is not necessarily the case. Many reactions involving change in composition or in molecular weight are included in this classification if characteristic atoms or groups of the original compounds are found in different orientations in the final products. Thus, a pinacol is converted into a pinacolone with loss of water. The change in composition and in molecular weight caused by the elimination of a molecule of water does not justify the withdrawal of this reaction from the category of rearrangements for the carbon radicals of the pinacol are present in the pinacolone, and the characteristic properties of the product which distinguish it from the original substance are due primarily to the new structural arrangements of these groups rather than to the slight change in composition.

The majority of the typical rearrangements are irreversible processes. Tautomeric changes and intramolecular neutralizations, therefore, are regarded as beyond the realm of this treatise. However, no sharp line marks the boundary between tautomerism and rearrangement. Many unimolecular reactions are upon the threshold of both domains. Some of them proceed virtually to completion in one way under a given set of conditions and in the reverse direction when the environment is changed. Examples of this kind have been included in a separate chapter on reversible processes that are commonly called rearrangements.

Although rate measurements indicate that rearrangements follow the unimolecular law, the actual mechanisms of some of these changes may involve a series of reactions some of which are bimolecular. It is the slowest reaction in a sequence that is measured and it is to this relatively slow change that the velocity constant applies. In some cases there is substantial evidence of more than one step in the conversion of a compound into an isomeric

form. In many cases, however, the reactions seem to be due to the direct exchange of places between two atoms or groups within a single molecule. Many chemists refuse to accept this idea. They are unwilling to assume that such a reaction can occur within a single molecule. At the Richmond meeting of the American Chemical Society (April, 1927) the concept of a direct interchange between two atoms in the same molecule was referred to, derisively, as the flip-flop theory.

Those who oppose the theory of direct exchange of groups within an isolated molecule seem to have no difficulty in accounting for similar exchanges between atoms or groups in different molecules. Yet to accomplish a double decomposition a collision between two molecules is a necessary antecedent. Every metathesis is an example of this type. Existing bonds must be broken and new ones established in either case. Of the two types of reactions the author regards the reaction within a single molecule as the simpler process, for in this case the reactive groups are carried along together. They are in positions favorable to the exchange as soon as the necessary energy is supplied. Even in the presence of a catalyst the formation of an ester from an alcohol and an acid is a slow process but the formation of a γ-lactone, which is a similar esterification process occurring within a single molecule, is too rapid for accurate measurement. In the case of photochemical rearrangements in gases the effective radiation may be absorbed by isolated molecules and the reaction may be completed without contact with other molecules or even with the walls of the containing vessel. When specific chemical reagents are required to cause a rearrangement, contact between the rearranging molecule and the activating agent is probably necessary. Only when an intermediate product is formed does a rearrangement become as complex as an ordinary double decomposition. Then, in either case, the reactive groups can exchange places only during the brief intervals of collision or close approach of two independently moving molecules.

In aqueous solution acetylchloroaminobenzene is converted by hydrogen chloride into *para*-chloroacetanilide. In a generally accepted theory of the mechanism of this reaction it is assumed that hydrolysis of the chloroamine, with the production of acetanilide and hypochlorous acid, is the first step. The production of chlorine from chloride ion and hypochlorous acids represents the second

step. Finally the chlorine acts upon acetanilide replacing the *para* hydrogen by the halogen. Thus by three orthodox maneuvers the flip-flop is avoided. The hydrolysis theory is probably correct as applied to the reaction in the presence of water, but a dry crystal of acetylchloroaminobenzene, in the absence of a catalyst or solvent, absorbs ultraviolet radiation and changes to *para*-chloroacetanilide. The mechanism involving a reaction with water and the formation of free chlorine can not possibly apply to this solid phase reaction. An unstable molecule may pass to a stable isomeric form by more than one path. Such possibilities have been pointed out in connection with many of the reactions set forth in these pages.

Molecular rearrangements are comparatively rare for the simple reason that the easy readjustments that can occur within a single molecule have been accomplished in the process of synthesis. As a rule we isolate a compound in a stable state. Many changes in the orientation of its atoms may have occurred with such velocities that the intermediates escape our notice. Occasionally we obtain a compound in a metastable condition. A change in the orientation of its atoms with a decrease in free energy is still possible. Such compounds undergo molecular rearrangements.

The course of the labile carbon radical has been followed in classifying these changes as migrations from one element to another. It is, of course, understood that in most cases there is a simultaneous transfer of some other radical in the reverse direction. An attempt has been made to review the more important types of rearrangements, to classify them on the basis of structural similarities, to present the principal theories relating to mechanisms and to supply an extensive bibliography.

C. W. Porter.

Berkeley, California.

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Chapter I

Migrations from Carbon to Nitrogen.

THE HOFMANN REARRANGEMENT OF AMIDES

Aliphatic and aromatic acid amides are converted into amines by treatment with chlorine or bromine and an alkali.

$$R-CO-NH_2 + Br_2 + 4KOH \longrightarrow$$
$$R-NH_2 + 2KBr + K_2CO_3 + 2H_2O.$$

Hofmann discovered this reaction and detected among the products an isocyanate.[1] A few years later Tiemann[2] showed that the isocyanate is an intermediate product in this synthesis, the amine being derived exclusively from the isocyanate by hydrolysis. The validity of this conclusion has been established experimentally in many laboratories.[3] In the amide the alkyl or aryl radical is attached to carbon. In the isocyanate the same radical is linked directly to nitrogen. This structural change is known as the Hofmann Rearrangement.[4]

As a typical example of procedure the method of preparing methylamine from acetamide may be outlined.

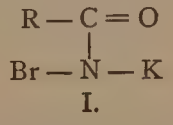
To a mixture of 25 grams of acetamide and 70 grams of bromine 2 *N* sodium hydroxide is added until the red color changes to a bright yellow. The mixture is then added slowly to 200 cc. of 6 *N* sodium hydroxide and heated to 70°C. until it becomes colorless. The time required for this part of the operation is usually thirty minutes and during this period the temperature should not go above 75°C. The methylamine is obtained from the solution by distillation with steam. It is collected in 6 *N* hydrochloric acid. After evaporation to dryness the methylamine hydrochloride is extracted from the solid residue with hot absolute alcohol.

The first product formed in the reaction is a bromoamide, RCONHBr, which can be isolated. An alkali acts upon this yield-

[1] Hofmann, *Ber.*, **15**, 407 (1882).
[2] Tiemann, *Ber.*, **24**, 4162 (1891).
[3] Stieglitz, *Am. Chem. J.*, **18**, 751 (1896); Mauguin, *Compt. rend.*, **149**, 790 (1909).
[4] For another reaction bearing Hofmann's name see p. 58.

ing hydrogen bromide and an isocyanate. In the presence of alcohol a urethane is formed.[5] A urethane, like an isocyanate, is readily hydrolyzed to an amine.

Hoogewerff and van Dorp advanced the earliest speculation concerning the mechanism of the Hofmann rearrangement.[6] They assigned to the alkali salt of the bromoamide the structure R—CO—NKBr and assumed that a salt of this constitution would rearrange if the radical, R, were more positive than the halogen.



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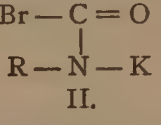
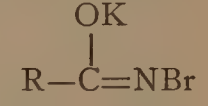
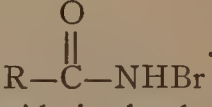


II.

The appearance of an isocyanate they believed to be due to the elimination of potassium bromide from the rearranged amide salt.

Although substantial support for this structure (formula I) of the salt has been offered by other chemists,[7] it is now generally assumed that the enol form of the amide prevails in its metallic derivatives.[8] The salt probably has the structure  while the parent substance is  . Mauguin obtained the sodium salt of acetobromamide in the dry state by adding to a cold alcoholic solution of sodium ethylate a chloroform solution of bromoacetamide. The salt was precipitated by diluting the solution with ether. When heated to 80° C. it decomposed rapidly. At room temperature the decomposition was slow. In either case the products were sodium bromide and methyl isocyanate.

The theory of Hoogewerff and van Dorp was weakened by the discovery that negative as well as positive groups would migrate[9] and it was finally abandoned because of its failure to correlate the rearrangements of bromoamides and of acid azides.

[5] Lengfeld and Stieglitz, *Am. Chem. J.*, **15**, 215, 504 (1893).

[6] Hoogewerff and van Dorp, *Rec. trav. chim.*, **6**, 373 (1887); **8**, 173 (1889).

[7] Ley and Kissel, *Ber.*, **32**, 1357 (1899); Mauguin, *Compt. rend.*, **149**, 790 (1909); Schroeter, *Ber.*, **42**, 2336 (1909); **43**, 2337 (1910); Jones, *Am. Chem. J.*, **48**, 1 (1912).

[8] Hantzsch and Dollfus, *Ber.*, **35**, 226 (1902); Stieglitz, *Am. Chem. J.*, **29**, 49 (1903); Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920).

[9] Van Dam, *Rec. trav. chim.*, **18**, 408 (1899); McCoy, *Am. Chem. J.*, **21**, 111 (1899); Van Dam and Aberson, *Rec. trav. chim.*, **19**, 318 (1900).

The possible formation of a triatomic ring as an intermediate was investigated by Hesse,[10] who found insufficient evidence to justify a claim in support of such a mechanism. The idea is represented by the following hypothetical reactions:

$$\underset{\text{I.}}{CH_3-CO-NHBr} \longrightarrow \underset{\text{II.}}{CH_2-CO-NH} \longrightarrow \underset{\text{III.}}{CH_3-N=CO}$$

Equally unsatisfactory is the suggestion of Nef [11] that the first step in the process consists of a dissociation into a methylene or phenylene type of radical, followed by reabsorption of the bivalent radical in a different position in the molecule.

In the course of an exhaustive study of the nitrile oxides Wieland [12] found that under certain conditions these compounds could be converted into isocyanates.

$$R-C(-O-)=N \longrightarrow R-N=C=O$$

On the basis of this reaction he suggested that a nitrile oxide might be an intermediate product in the Hofmann, Curtius and Beckmann rearrangements as follows:

$$R-C(ONa)=NBr \longrightarrow R-C(-O-)=N + NaBr$$

$$R-C(=O)-N<(=N-) \longrightarrow R-C(-O-)=N + N_2$$

$$R_2C=NOH \longrightarrow R_2C(-O-)-NH$$

Wieland conducted many experiments to obtain evidence in support of this mechanism but finally abandoned the idea and accepted the views of Stieglitz, L. W. Jones and Schroeter.[13]

A very fruitful theory concerning the mechanism of the Hofmann rearrangement has developed from the suggestion that an amide is converted into an amine through the formation of an unstable intermediate product containing univalent nitrogen.[14]

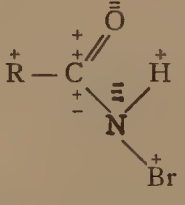
[10] Hesse, *Am. Chem. J.*, **29**, 65 (1903).
[11] Nef, *Ann.*, **298**, 202 (1897); **318**, 1, 137 (1901).
[12] Wieland, *Ber.*, **40**, 1667 (1907); **42**, 803, 4207 (1909).
[13] Schroeter, *Ber.*, **42**, 2336, 3356 (1909).
[14] Tiemann, *Ber.*, **24**, 4162 (1891).

Positive evidence for the existence of such an intermediate can hardly be expected, for any compound of univalent nitrogen would be too unstable to permit isolation.

Over a period of twenty years Stieglitz and his co-workers investigated this problem and their valuable contributions [15] have made it evident that the Hofmann, Beckmann and Curtius rearrangements are fundamentally alike. They are special applications of a general reaction which probably involves the transient existence of a compound of univalent nitrogen, and which results in the ultimate migration of an alkyl or an aryl radical from carbon to nitrogen.

An application of the electron theory to the Stieglitz formulation of the rearrangement was made by Jones.[16]

The electronic structure of the acylhalogenamine (bromamide) is indicated by the formula:



In the earlier applications of this theory it was assumed that the establishment of a chemical bond between two atoms was accomplished by the complete transfer of an electron from one of the atoms to the other. The atom which had lost the electron was then thought of as a positively charged unit in the molecule. The member to which the electron had passed was represented as a negatively charged atom. The Lewis conception of valence is now quite generally accepted and a chemical bond is represented as due to the sharing of a pair of electrons by the two atoms concerned. In a strictly non-polar compound the electrons are shared equally. They are stationed midway between the two atoms. If the two atoms differ in their tendencies to yield or acquire electrons the compound displays polar characteristics and the bond is represented

[15] Slosson, *Ber.*, **28**, 3265 (1895); Stieglitz and Slosson, *Ber.*, **34**, 1613 (1901); Gräbe and Rostovzeff, *Ber.*, **35**, 2744 (1902); Stieglitz and Earle, *Am. Chem. J.*, **30**, 399 (1903); Stieglitz, *J. Am. Chem. Soc.*, **30**, 1797 (1908); Stieglitz and Peterson, *Ber.*, **43**, 782 (1910); Peterson, *Am. Chem. J.*, **46**, 325 (1911); Stieglitz and Vosburgh, *Ber.*, **46**, 2151 (1913); Stieglitz, *Proc. Nat. Acad. Sci.*, **1**, 196 (1915).

[16] Jones, *Am. Chem. J.*, **48**, 1 (1912); **50**, 440 (1913); Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272 (1914).

by a pair of electrons still shared by the two atoms but drawn from the central position toward the electronegative atom. In an electrolyte the electron pair becomes the exclusive property of the negative ion. The gradation from a non-polar to a completely ionized compound may be represented by the following formulas in which A and B stand for two atoms in chemical union and the small circles represent valence electrons.

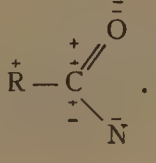
A : B A :B A :B

Stieglitz has suggested that we retain the plus and minus signs to represent even the slightest displacement of the electron pair from the central position. It is in this sense that the plus and minus signs are used throughout this book. These signs no longer imply complete polarity. They indicate only relatively positive and negative states. It would be possible to represent the electrochemical characters of A and B by using light and heavy signs as follows:

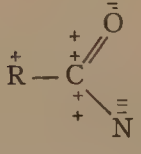
AB $\overset{+}{A}\overset{-}{B}$ $\overset{+}{\underset{\cdot}{A}}\overset{-}{B}$

This is generally unnecessary. No attempt to define exactly the electrochemical properties of atoms by light or shaded symbols will be made. With this explanation of the new meaning of plus and minus signs we may proceed to the electronic representation of the Hofmann rearrangement.

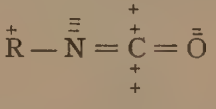
In the formula for bromoacetamide given above a positive charge is assigned to the bromine atom. It is introduced into the amido group through the agency of a hypobromite and it yields hypobromous acid on hydrolysis. An unstable intermediate is derived from the bromoamide by loss of hydrogen bromide. This reaction is favored by the presence of an alkali. The bromine which was introduced into the amide as the positive ion of a hypobromite appears among the reaction products as a bromide ion. The conversion of $\overset{+}{Br}$ to $\overset{-}{Br}$ involves the shift of two electrons from the nitrogen toward the bromine atom. The complete removal of the bromine as bromide ion leaves a compound of univalent nitrogen having the structure:



It is this compound that rearranges. The free valences of the nitrogen atom are powerful enough to cause a reconstruction of the molecule. Or, to state the same thing in other words, the nitrogen atom in the state represented by the above formula has a strong tendency to acquire electrons. It is assumed that two electrons are drawn from the carbon toward the nitrogen atom, leaving a structure in which the carbonyl carbon is more completely oxidized.



The radical, $\overset{+}{R}$, will no longer be held by the positive carbon. It migrates to the nitrogen, forming an isocyanate.



This theory of the Hofmann rearrangement is supported by very good evidence. Slosson found it impossible to induce the rearrangement in acyl-alkyl-halogen amines, RCONRBr, or in the corresponding aryl derivatives. From these compounds it would be necessary to remove an alkyl or an aryl halide in order to obtain the unstable imide and no available reagent accomplishes this. For the same reason the chloroimido esters fail to rearrange.

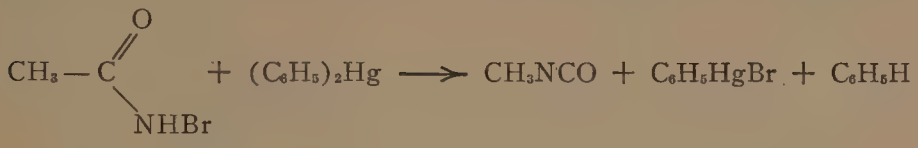
On the other hand, the loss of nitrogen from an acid azide leads directly to the formation of the same radical that is obtained from a bromoamide by removal of hydrogen bromide and these compounds yield isocyanates when heated. Similarly the hydroxamic acids lose water with the production of isocyanates.

In forming an isocyanate the migrating radical becomes attached to nitrogen through the same valence bond that was released in breaking the carbon to carbon linkage. Thus when *meta*-bromobenzamide is treated with an alkaline hypobromite solution *meta*-bromophenyl*iso*cyanate is produced in spite of the strong tendency of bromine to compel substitution in an *ortho* or *para* position.[17]

Mercury biphenyl acts upon N-bromoacetamide in dry benzene

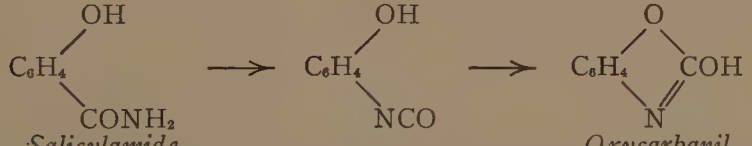
[17] Beckmann and Correns, *Ber.*, **55**, 848 (1922).

when heated or when exposed to sunlight, producing methyl*iso*-cyanate.[18]



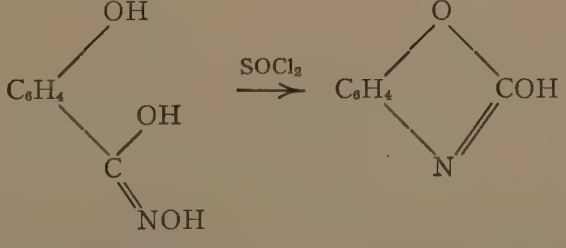
Mercury biphenyl in benzene acts as sodium hydroxide does in aqueous solution or sodium ethylate in absolute alcohol. And just as these reagents fail to cause a rearrangement in N-substituted alkyl or aryl bromamides so mercury biphenyl fails to act upon them in dry benzene. Kharasch regards this as evidence that mercury biphenyl is a base in the benzene system as sodium amide is in ammonia and as calcium oxide is in the water system. Kharasch proved the presence of methyl*iso*cyanate in the reaction mixture by adding dry aniline and obtaining methyl phenylurea.

An isocyanate reacts with an alcohol or a phenol by addition, forming a urethane, or with an amine, forming a substituted urea. When the two groups which are capable of this addition are present in the same molecule, ring formation occurs. Thus, salicylamide is converted by bromine and an alkali into oxycarbanil.



Salicylamide *Oxycarbanil*

Salicylhydroxamic acid, when warmed with sulfur oxychloride, yields the same product.[19]

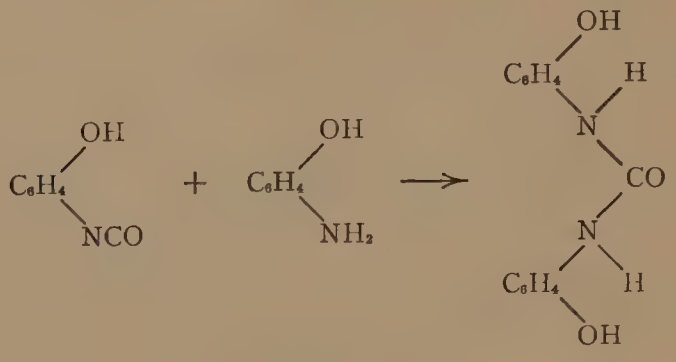


In each of the cases mentioned in the last paragraph, dihydroxyphenylurea is formed as a by-product. Some of the hydroxyphenyl-

[18] Kharasch, *J. Am. Chem. Soc.*, **43**, 1888 (1921).

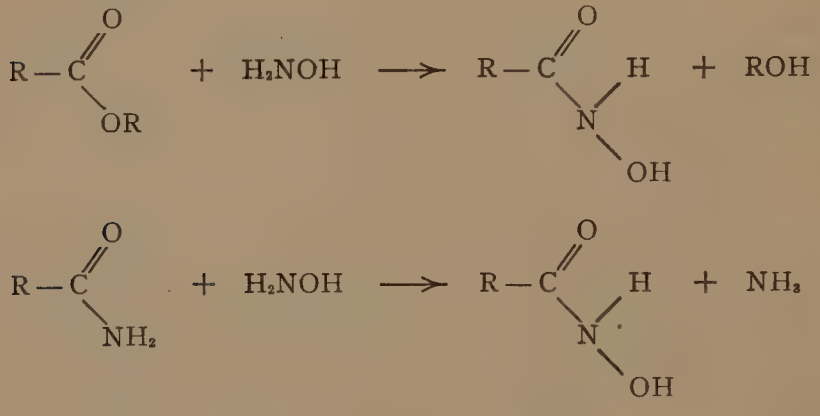
[19] Marquis, *Compt. rend.*, **143**, 1163 (1906). Marquis does not consider isocyanate a necessary intermediate. Scott and Mote, *J. Am. Chem. Soc.*, **49**, 2545 (1927). Scott and Mote used an ester of salicylhydroxamic acid. They did not detect an isocyanate as an intermediate but they admitted the possibility of its transient existence.

*iso*cyanate is hydrolyzed to *ortho*-aminophenol and the following addition occurs:



HYDROXAMIC ACIDS

The hydroxamic acids are crystalline solids. They are prepared from esters, acid anhydrides, acid chlorides or amides in inert solvents by treatment with hydroxylamine.[20]



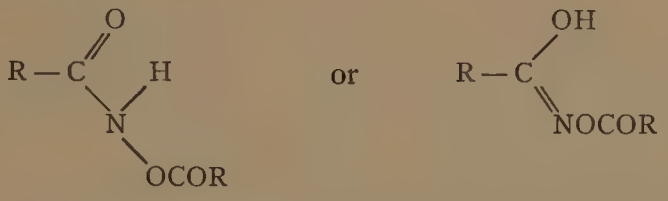
They have been made also from nitroparaffins by a method which Bamberger describes as involving the migration of an oxygen atom.[21]

The hydroxamic acids of β-acylhydroxylamines and their esters present the phenomenon of tautomerism as do the amides. Preference has usually been given to the enol form in writing structural formulas of salts and esters of these acids but in cases where

[20] Lossen, *Ann.*, **150**, 314 (1869); **161**, 347 (1872); **175**, 320 (1875); Hofmann, *Ber.*, **22**, 2854 (1889); *Jeaurenaud, Ber.*, **22**, 1270 (1889); Miolati, *Ber.*, **25**, 700 (1892); Jones and Neuffer, *J. Am. Chem. Soc.*, **39**, 659 (1917); Jones and Werner, *ibid.*, **39**, 413 (1917); Jones and Sneed, *ibid.*, **39**, 668, 674 (1917).

[21] Bamberger, *Ber.*, **35**, 45 (1902).

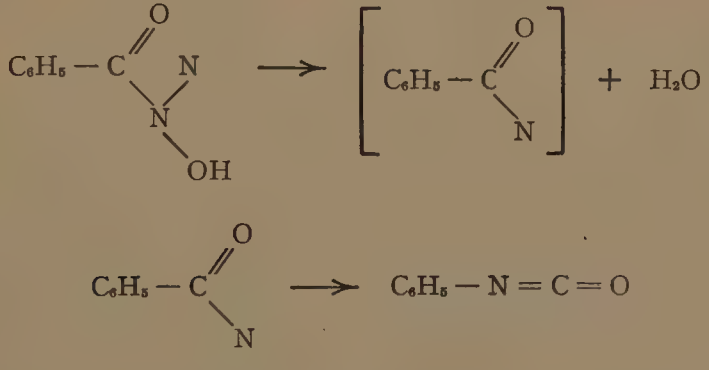
isomeric derivatives are unknown the single isolated salt, ester, or free acid may be written in either way. An ester, for example, may be written:



Lossen [22] observed that when the acetyl derivative of a hydroxamic acid is warmed with an alkali an isocyanate is formed. The metallic derivatives of the esters of hydroxamic acids are very susceptible to this change.

The most satisfactory generalization concerning the mechanism of the reaction is one which assumes the transient existence of a compound of univalent nitrogen.

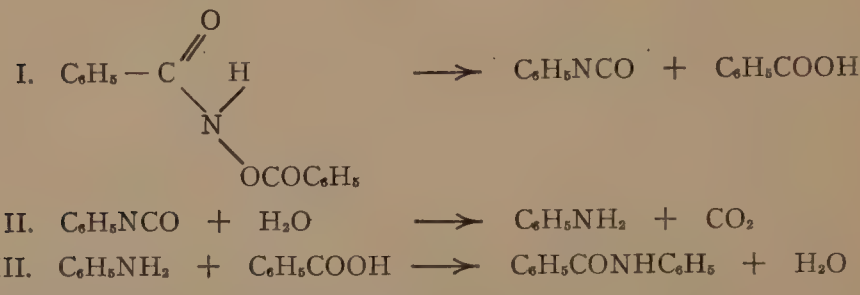
The rearrangement is formulated by Jones and by Stieglitz as follows:



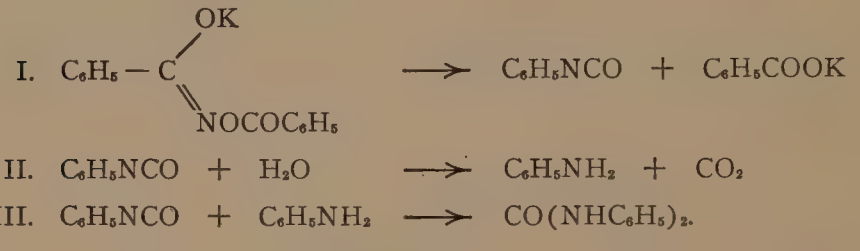
Many results obtained by the earlier chemists and recorded by them without any attempt at correlation can be explained, or at least classified, as examples of the Beckmann rearrangement. Thus Pieschel [23] found that the benzoyl ester of benzhydroxamic acid, when warmed alone, yields phenyl isocyanate, benzoic acid, benzanilide and carbon dioxide. The simplest explanation of this observation is that the initial change consists of the elimination of benzoic acid. This is followed by the shift of a phenyl group from carbon to nitrogen and the hydrolysis of a part of the isocyanate

[22] Lossen, *Ann.*, **186**, 1 (1877); **252**, 170 (1889); **281**, 169 (1894).
[23] Pieschel, *Ann.*, **175**, 305 (1875).

to carbon dioxide and aniline. Finally, the aniline reacts with benzoic acid to form benzanilide.



Boiling water converts the potassium salt of the ester into diphenylurea, potassium benzoate and carbon dioxide.[24] This result, which was not understood when the fact was recorded, can be explained in the same way.[25]



In the presence of alcohol urethane is formed instead of diphenylurea, a result in harmony with the observation that bromoamides when heated with sodium alcoholate yield urethanes.

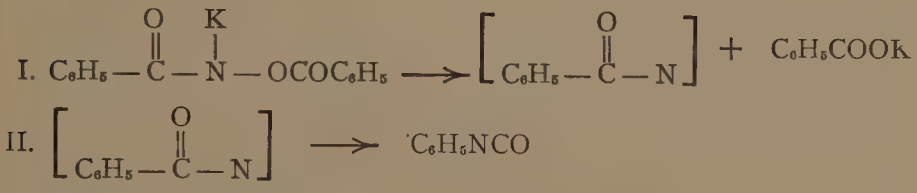
L. W. Jones has prepared and examined a great variety of hydroxamic acid derivatives. Some of these, even when dry and in the solid state, have decomposed with explosive violence and the products have indicated the usual migration of an alkyl or aryl radical from carbon to nitrogen.

The dynamics of the rearrangement of the potassium salt of dibenzhydroxamic [26] acid was studied by Dougherty and Jones,[97] who found the velocity of the rearrangement to correspond with that of a unimolecular reaction for the last 75% of the reaction time. Very dilute solutions were used and the temperature was held at 25° C. to obtain conditions under which the reaction would

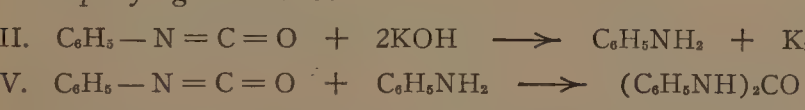
[24] Lossen and Rothmund, *Ann.*, **175**, 257 (1874).
[25] Stieglitz and Stagner, *J. Am. Chem. Soc.*, **38**, 2046 (1916).
[26] Acyl esters of hydroxamic acids are called dihydroxamic acids.
[27] Dougherty and Jones, *J. Am. Chem. Soc.*, **46**, 1535 (1924).

not be completed within one hundred hours.[28] They outline the reactions as follows:[29]

Rearrangement:



Accompanying reactions:



Under the conditions of the experiment no apparent change occurred during the first fifteen hours. Then a purple color developed and the odor of phenyl*iso*cyanide was noticed. This result was hardly to be expected in a reaction which certainly yields phenyl*iso*cyanate as the chief intermediate product. The reaction mixture gave tests for aniline and for monobenzhydroxamic acid almost from the beginning. Symmetrical diphenylurea began to precipitate after twenty-five hours. Reactions III and IV are very rapid and could not interfere with measurements relating to the slower rearrangement. As stated by Dougherty and Jones:

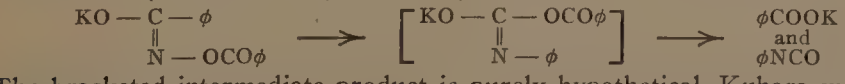
"Hydrolysis of the potassium dibenzhydroxamate is the only side reaction which could appreciably affect the measurement of the rate of rearrangement. Since the reaction could be stopped at any time by the addition of a mineral acid, and the unchanged dibenzhydroxamic acid could be precipitated practically quantitatively from the solution of its potassium salt, it was possible to measure the rate at which the dibenzhydroxamic acid itself was being consumed in the rearrangement and in the accompanying side reactions. When the figures obtained in this way were inserted in the equation for a first order reaction, it was found that a diminishing value for K was obtained for a period of 25 hours, at the beginning of the reaction."

"Beyond that stage, during approximately 75 per cent of the course of the reaction, a fairly satisfactory constant was obtained."

Factors that influence the rearrangement after the compound of univalent nitrogen has been formed have been investigated by

[28] At 70°C. the reaction is completed within two hours. Mohr, *J. prakt. Chem.*, **71**, 133 (1905).

[29] Kuhara (*J. Chem. Soc.*, **106**, 1538) outlines the reaction as follows:



The bracketed intermediate product is purely hypothetical. Kuhara was not able to isolate it.

L. W. Jones and his students. An important generalization based upon their observations is that the "ease of rearrangement is dependent upon the tendency of the radical in the univalent nitrogen derivative to exist as a free radical." [30] For example, triphenylmethyl is capable of independent existence but monophenylmethyl and diphenylmethyl have never been isolated. In comparing the conditions required to cause rearrangements in triphenylacethydroxamic acid, $(C_6H_5)_3C—CO—NHOH$, and diphenylacethydroxamic acid, $(C_6H_5)_2CH—CO—NHOH$, it was found that esters of the former, in which the migrating radical is triphenylmethyl, undergo the Lossen change with remarkable ease. The diphenylmethyl derivative is much more stable.

Tetraphenylhydrazine yields the free radical $(C_6H_5)_2N—$ and Hurd [31] found that derivatives of N-diphenyl-N-hydroxyurea $(C_6H_5)_2N — CO — NHOH$,[32] rearrange readily at room temperature. On account of the tendency to rearrange, the sodium and potassium salts of the esters of this hydroxamic acid could not be isolated in a pure state. In every case the salt of the ester is the most reactive derivative. In the experiment referred to above, Hurd used the sodium salt of the acetyl derivative and obtained results indicated by the following equations:

$$(C_6H_5)_2N—CO—N<\begin{matrix}Na\\OCOCH_3\end{matrix}$$

$$\downarrow$$

$$[(C_6H_5)_2N—CO—N] + CH_3COONa$$

$$\downarrow$$

$$(C_6H_5)_2N—N=CO \xrightarrow{H_2O} (C_6H_5)_2N—NH_2 + CO_2$$

The corresponding monophenylcarbamhydroxamic acid derivatives could not be made to rearrange.

In further support of the theory that radicals capable of independent existence have the greatest tendency to migrate, we have the results of experiments with hydroxamic acids which are isomeric with triphenylacethydroxamic acid.[33] In *ortho* and *para*

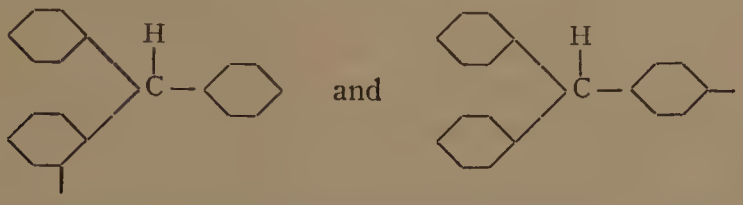
[30] Jones and Hurd, *J. Am. Chem. Soc.*, **43**, 2422 (1921); Jones and Root, *ibid.*, **48**, 181 (1926).

[31] Hurd, *J. Am. Chem. Soc.*, **45**, 1472 (1923).

[32] This compound is known also as α, α-diphenyl-β-hydroxyurea and as diphenylcarbamhydroxamic acid.

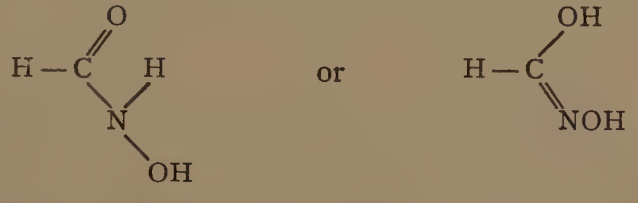
[33] Jones and Root, *J. Am. Chem. Soc.*, **48**, 181 (1926).

benzhydrylbenzhydroxamic acids the radicals which must migrate in a Lossen rearrangement have the structures:



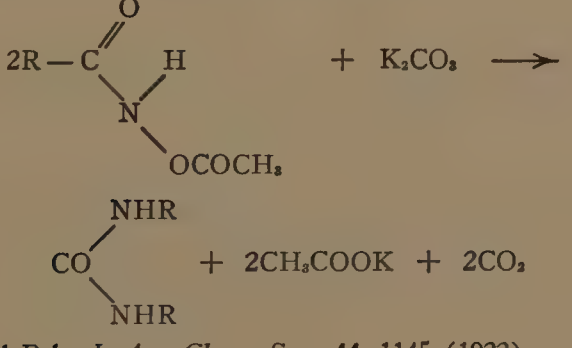
These radicals are isomeric with triphenylmethyl, yet when either of them is substituted for trpihenylmethyl in an ester of triphenylacethydroxamic acid, the rearrangement occurs only upon heating to 100° C. The triphenylmethyl radical shifts to nitrogen at room temperature.

Formhydroxamic acid, m.p. 82° C., corresponding to one of the following structures,



explodes when heated to a temperature above its melting point. The decomposition products are carbon monoxide and hydroxylamine. But in aqueous alkaline solution it undergoes the rearrangement yielding water, carbon dioxide and ammonia.

The behavior of unsaturated hydroxamic acids derived from oleic, elaidic and ricinoleic acids have been investigated by Nicolet and Pelc.[34] In every case the usual Lossen rearrangement occurred when the monoacetyl derivative of the hydroxamic acid was warmed for thirty minutes with dilute aqueous or alcoholic alkali. Substituted ureas or urethanes were isolated.



[34] Nicolet and Pelc, *J. Am. Chem. Soc.*, **44**, 1145 (1922).

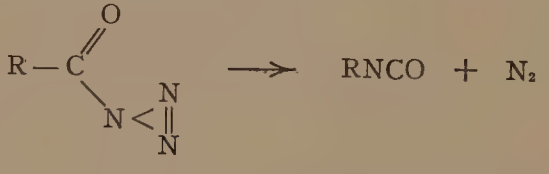
A change occurred in connection with the double bond when oleohydroxamic acid or elaidohydroxamic acid was converted into an isocyanate through the agency of warm acetic anhydride. Beginning with either of these acids, a mixture of *cis* and *trans* heptadecylenyl*iso*cyanates was obtained. The double bond was not affected when the rearrangement was induced under conditions that gave rise to ureas or urethanes, but was affected when the reaction was carried out in such a way as to yield an isocyanate as a final product. This seems to challenge our assumption that the isocyanate is an intermediate product in the Lossen and the Stieglitz rearrangements.

Oleohydroxamic acid was prepared by heating for two hours under a reflux condenser a mixture of (a) 15 grams of hydroxylamine hydrochloride in 100 cc. of alcohol, (b) 9.2 grams of sodium in 100 cc. of alcohol, (c) 62 grams of ethyl oleate in 200 cc. of alcohol. Most of the alcohol was then distilled off and the residue was acidified with 15 per cent hydrochloric acid. The precipitated hydroxamic acid was recrystallized from alcohol or acetone.

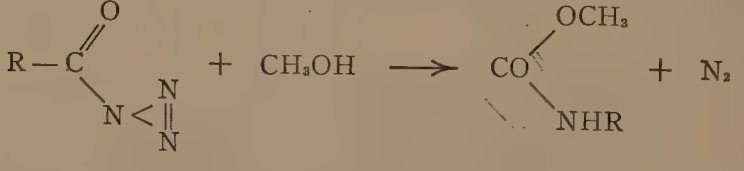
In the rearrangement of *cis* and *trans* forms of an acid azide only one product is obtained. The labile form is converted into the more stable structure during the course of the reaction.[35]

AZIDES

By the application of heat an acid azide is changed quantitatively to nitrogen and an isocyanate.



In the presence of an alcohol, a urethane is formed.



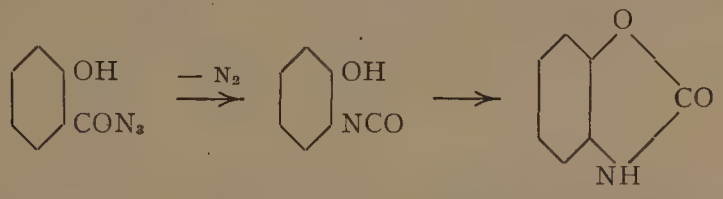
Azides are prepared from acid chlorides in inert solvents by the action of sodium azide. If the mixture is warmed, an isocyanate can be obtained without the necessity of isolating the intermediate acyl azide.

[35] Jones and Mason, *J. Am. Chem. Soc.*, **49**, 2528 (1927).

Methyl*iso*cyanate was made by adding 15.5 grams of acetyl chloride to a cold amyl ether solution of sodium azide.[36] When the solution was warmed to 60°C. or 70°C., nitrogen was evolved. The yield of methyl *iso*cyanate, after fractionating to obtain a preparation boiling at 42°C.-43°C. was 10 grams.

Stoermer [37] and his pupils prepared azides from many aromatic acids and found that each of them gave up two-thirds of its nitrogen when heated. Benzazide, when heated alone at 80° C., decomposed explosively, but when dissolved in dry benzene or toluene and warmed on a water bath, nitrogen was evolved quietly and at a measurable rate.

From *ortho*-hydroxybenzazide an inner urethane is obtained.[38]



The rearrangement is followed by the ordinary addition reaction between a phenol and an isocyanate but, in this case, the two reactive groups are in the same molecule.

Not only the acid azides but hydrocarbyl azides undergo the Curtius rearrangement.[39] Thus, for example, benzylazide yields phenylmethylene amine and nitrogen.

$$C_6H_5CH_2N_3 \longrightarrow C_6H_5CH_2N< + N_2$$
$$\downarrow$$
$$C_6H_5N=CH_2$$

Hydrogen, instead of the phenyl group, may migrate, for in this reaction benzylidene imide was obtained as a by-product.

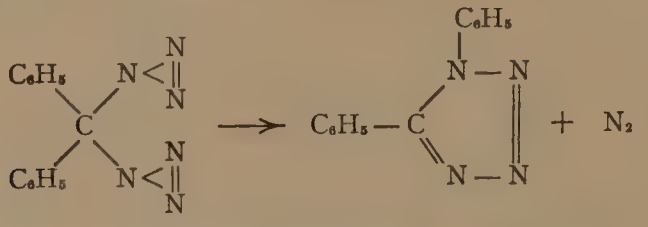
$$C_6H_5-CH_2-N< \longrightarrow C_6H_5-CH=NH$$

On hydrolysis, the latter yields benzaldehyde and ammonia, and these products were isolated.

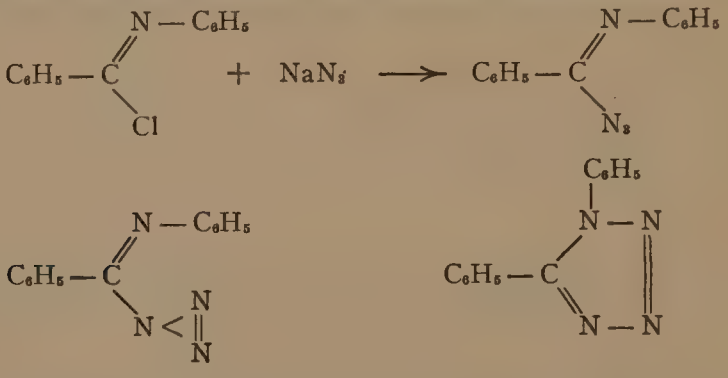
A diazide (diphenylmethanediazide) can be obtained from benzophenone chloride by treatment with sodium azide in amyl ether.[40] When heated to 150° C. in a current of carbon dioxide

[36] Schroeter, *Ber.*, **42**, 3356 (1909); *see also* Schroeter and Sondag, *Ber.*, **41**, 1921 (1908).
[37] Stoermer, *Ber.*, **42**, 3133 (1909).
[38] Struve and Radenhausen, *J. prakt. Chem.*, **52**, 241 (1895).
[39] Curtius, *J. prakt. Chem.* (2) **63**, 428 (1901); Curtius and Darapsky, *Ber.*, **35**, 3229 (1902).
[40] Schroeter, *Ber.*, **42**, 2336, 3356 (1909).

it decomposes with a steady evolution of nitrogen and the production of a diphenyltetrazole.



The structure of the final product was established by its synthesis from phenylimidebenzyl chloride and sodium azide.



This course of the reaction was confirmed by the independent work of Forster [41] on benzhydroxamic chloride.

In an attempt to duplicate these results in the aliphatic series it was found that the action of phosphorus pentachloride on the ketone gave rise to a monohalogen derivative of an unsaturated hydrocarbon. This was due to the easy removal of hydrogen chloride from the dichloride.

$$C_6H_5 - CCl_2 - CH_3 \longrightarrow C_6H_5 - CCl = CH_2 + HCl$$

To avoid this difficulty a ketone having a tertiary alkyl radical was used. Pivalophenone proved to be a suitable compound. Pivalophenone reacts with phosphorus pentachloride at 140° C.-160° C., yielding the dichloride as a colorless oil which boils at 118° C.-120° C. under 10 mm. pressure.

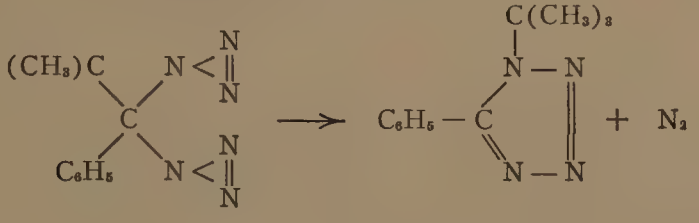
$$(CH_3)_3C - CO - C_6H_5 + PCl_5 \longrightarrow$$
$$(CH_3)_3C - CCl_2 - C_6H_5 + POCl_3$$

The products are separated by distillation under reduced pressure.

Pivalophenone chloride, when mixed with silver azide in amyl

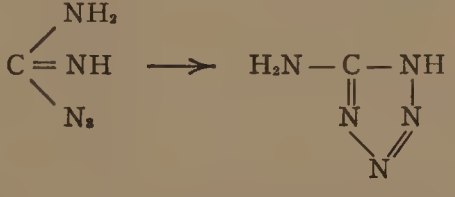
[41] Forster, *J. Chem. Soc.*, **95**, 184 (1909).

ether and heated on a paraffin bath to 120° C. yields nitrogen and C-phenyl-N-tertiarybutyltetrazole.



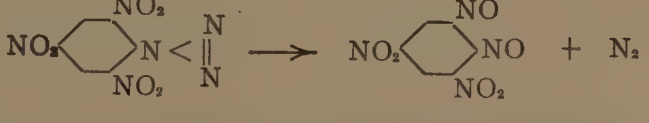
A 60% yield was obtained. The failure to make a complete transformation was attributed to the inactivity of silver azide when it becomes coated with silver chloride.[42]

Guanyl azide, prepared by Thiele from guanidine and hydrazoic acid [43] isomerizes irreversibly to 5-aminotetrazole.[44]



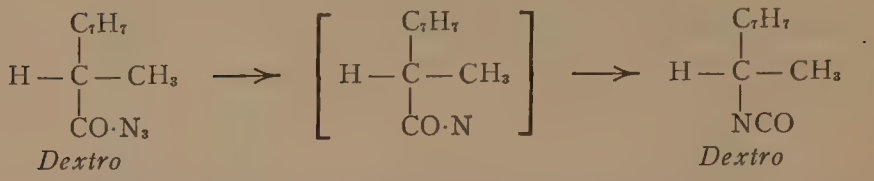
The change is induced by treatment with water or a dilute acid. It occurs slowly at room temperature.

A case involving the migration of oxygen from a nitro group to an ortho univalent nitrogen was discovered by Schrader.[45] Picryl chloride reacts with sodium azide forming picryl azide and the latter, when heated, yields nitrogen and 1,2-dinitroso-4,6-dinitrobenzene.

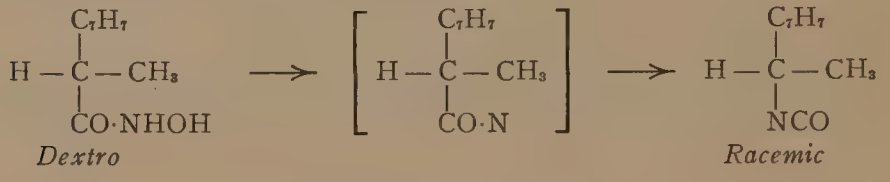


An asymmetric group can exist without racemizing during the interval required for rearrangement.[46] The optically active d-benzylmethylacetazide, when dissolved in benzene at 35° C., changes rapidly, but at a measurable rate, into nitrogen and *d*-benzylmethyl-methyl*iso*cyanate.

[42] Schroeter, *Ber.*, **44**, 1201 (1911).
[43] Thiele, *Ann.*, **270**, 1 (1892).
[44] Hantzsch and Vagt, *Ann.*, **314**, 339 (1901). C. V. Hart, *Thesis*, Stanford University (1927).
[45] Schrader, *Ber.*, **50**, 777 (1917).
[46] Jones and Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).



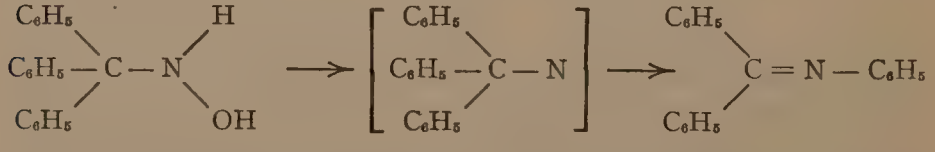
On hydrolysis the isocyanate yields an optically active amine and with ammonia it forms an optically active mono-substituted urea. The corresponding *d*-benzylmethyl-acethydroxamic acid and its esters rearrange with racemization.



TRIARYLMETHYLAMINES

Triphenylmethylhydroxylamine is characterized by a structure which, through loss of water, should yield a derivative of univalent nitrogen. A triphenylmethylhalogenamine through elimination of halogen and triphenylmethyldichloroamine by loss of chlorine should yield the same product. If the production of univalent nitrogen leads to rearrangement in oximes and in amides these derivatives of triphenylmethylamine should display similar tendencies. To test this generalization Stieglitz prepared these compounds and subjected them to appropriate treatment for the production of the hypothetical nitrogen compound.

When triphenylmethylhydroxylamine was warmed with phosphorus pentachloride it was converted into benzophenone phenylimide.

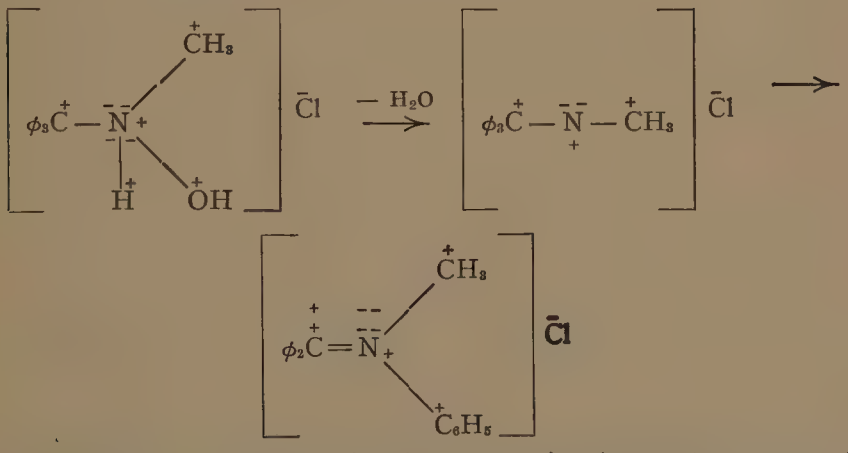


A similar result was achieved by removal of hydrogen bromide from triphenylmethylbromoamine [47] and by removal of chlorine from triphenylmethyldichloroamine.[48] Removal of the halogen acid was accomplished by heating the amine with a base. Chlorine was removed from the dichloroamine by heat alone. The migra-

[47] Stieglitz and Vosburgh, *Ber.*, **46**, 2151 (1913).
[48] Stieglitz et al., *Proc. Nat. Acad. Sci.*, **1**, 202 (1915).

tion of an aryl group from the triarylmethyl radical to the nitrogen atom in compounds of this type is known as the Stieglitz rearrangement.

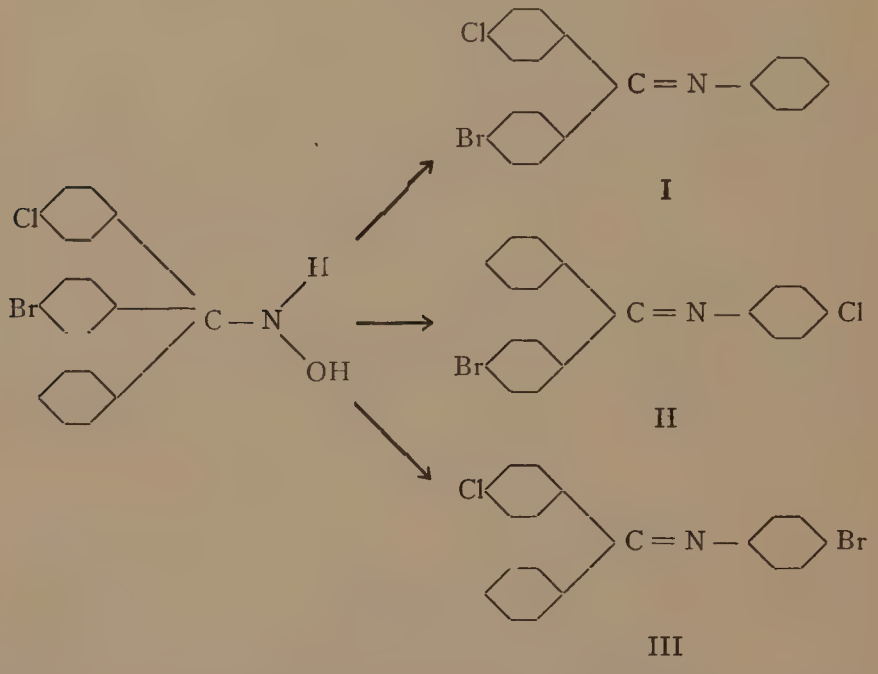
β-Triphenylmethyl-β-methylhydroxylamine should not rearrange if a univalent nitrogen compound is a necessary intermediate, for neither a base nor a dehydrating agent should remove methyl alcohol from this compound. It was found, however, that phosphorus pentachloride converts β-triphenylmethyl-β-methylhydroxylamine into a product which, on hydrolysis, yields methylaniline, and this could be formed only through the migration of a phenyl group from carbon to nitrogen. The dehydration of a salt of this hydroxylamine would leave a compound in which the electronic structure corresponds closely to that of a univalent nitrogen compound and the rearrangement is accordingly represented as taking the following path:[49]



Substitution of halogen for hydrogen in the aryl groups of a triarylmethylhydroxylamine does not influence the course of the

[49] Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272 (1914); Stieglitz, Reddick and Leech, *Ber.*, **46**, 2147 (1913). The formulation of the reactions appears in a slightly different form in these papers. The newer interpretation given here is authorized in a private communication. (Stieglitz to Porter, March 8, 1928.) The lines commonly used to represent chemical bonds are retained here to make the formulas conform to the plan followed throughout the book, but it should be remembered that the single bond (represented by one line) means a pair of electrons shared by the two atoms. A double bond means that the two atoms, so united, are sharing two pairs of electrons. The plus and minus signs no longer imply a complete transfer of an electron from one atom to another. They indicate merely a displacement of the pair of valence electrons from the central position. Chemical union between the atoms is, in this case, still due to the sharing of electrons, but it is not an equal sharing. One of the atoms is rendered negative with respect to the other even though the electron displacement be extremely slight. See p. 16.

reaction. Chlorobromotriphenylmethylhydroxylamine yields three products when warmed with phosphorus pentachloride.

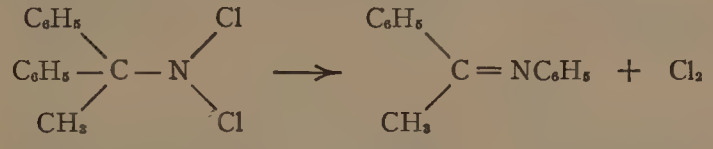


Approximately equal quantities of the three products are obtained as would be expected under the assumption that the substituted and unsubstituted aryl groups are equally free to move.[50]

The relative velocities with which alkyl and aryl radicals migrate in this type of change was investigated by Neff.[51] An attempt was made to connect the rates of migration with the electronic structures of the molecules. A non-polar bond is represented by a pair of electrons midway between two atoms. Partial polarity is shown by the electron pair nearer to one than the other of the combined atoms, and ionization by a complete separation of the charged groups. The relative polarities of groups in the compounds investigated were estimated from the dissociation constants of acids containing these groups. In the acid RCOOH the nearer the electron pair approaches R the more positive will the C become and the greater will be the tendency for the compound to yield hydrogen ions. By the same process of reasoning the conclusion is reached that the nearer the electron pair approaches R the

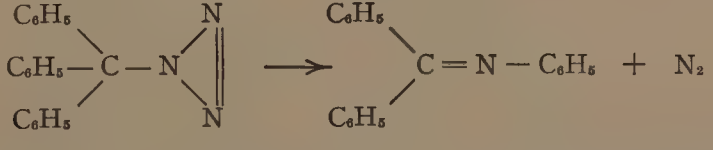
[50] Morgan, *J. Am. Chem. Soc.*, **38**, 2095 (1916).
[51] Neff, *Thesis*, University of Chicago (1927).

more readily will R migrate from carbon to some other position in the molecule. Benzoic acid is stronger than acetic acid ($K = 6.6 \times 10^{-5}$ and 1.8×10^{-5} respectively). Neff concludes that the phenyl group should migrate in preference to the methyl group when both are attached to the same carbon atom. In harmony with this view is the fact that methyldiphenylmethyldichloroamine, when heated, yields chlorine and phenylimido-acetophenone.

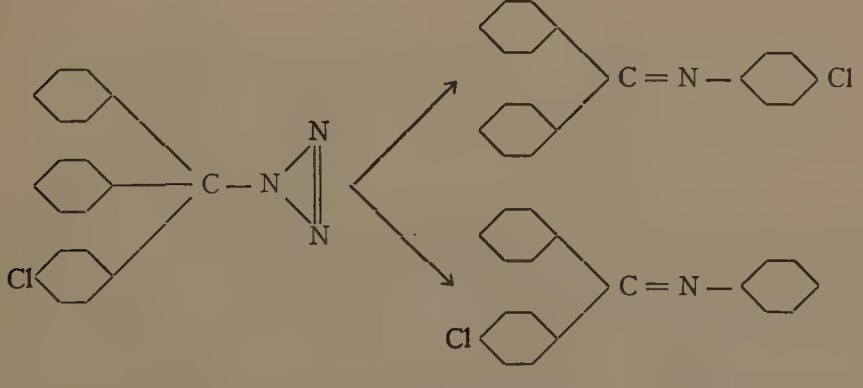


Other support for the theory is found in the reactions of some hydroxamic acids.[52] Montagne's observation that the radical $CH_3C_6H_4-$ migrates more readily than does ClC_6H_4- is contrary to the expectation for the dissociation constants of the acids *p*-$CH_3C_6H_4COOH$ and *p*-ClC_6H_4COOH are 4.5×10^{-5} and 9.3×10^{-5} respectively.

Triphenylmethylazides rearrange under the influence of heat alone.[53]



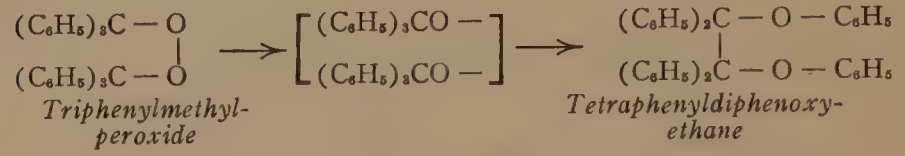
Two products were obtained from *para*-chlorotriphenylmethylazide:



Triphenylmethylhydrazine, $\phi_3C-NH-NH-C\phi_3$, does not rearrange but triphenylmethylperoxide, $\phi_3C-O-O-C\phi_3$ is con-

[52] Jones and Hurd, *J. Am. Chem. Soc.*, **43**, 2422 (1921).
[53] Stieglitz and Senior, *J. Am. Chem. Soc.*, **38**, 2718 (1916).

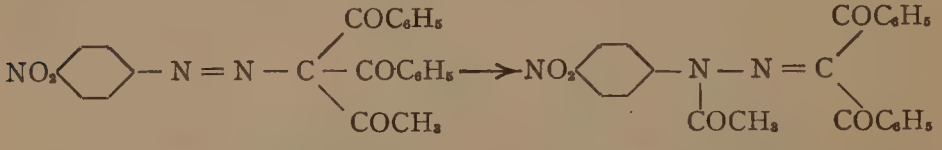
verted into tetraphenyldiphenoxyethane.[54] Wieland believes the preliminary step is a dissociation between the two oxygen atoms which is followed by the migration of a phenyl group to oxygen in each of the unsaturated radicals. Finally the radicals recombine as indicated below.



Triphenylmethyl-peroxide — *Tetraphenyldiphenoxy-ethane*

AZO COMPOUNDS

p-Nitrobenzene-azo-acetyldibenzoylmethane, an orange colored compound melting at 110.5° C., is changed to a colorless isomer melting at 201° C. when the pure compound alone is heated to a temperature above its melting point. The reaction is a general one for triacylmethyl-azo-compounds and the product formed in each case is an acyl derivative of a hydrazone.[55]



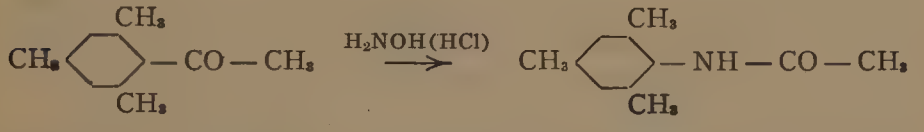
In this case the acetyl, rather than a benzoyl group, migrates, but the benzoyl radical will shift if no lighter acyl group is present.

THE BECKMANN REARRANGEMENT OF OXIMES

The oximes or isonitroso-compounds are prepared from aldehydes and ketones by treatment with hydroxylamine. They may be made also through the action of nitrous acid upon compounds having methylene groups in which the hydrogen atoms are rendered active by the proximity of negative radicals. Aldehydes react with hydroxylamine more readily than do ketones. Some of the latter require prolonged heating in an autoclave with a hydroxylamine salt and an excess of alkali. The reaction is reversible, the oximes being readily hydrolyzed in the presence of acids. Rate measurements have been made on oxime formation in connection with many types of ketones.[56] In the case of benzophenone,

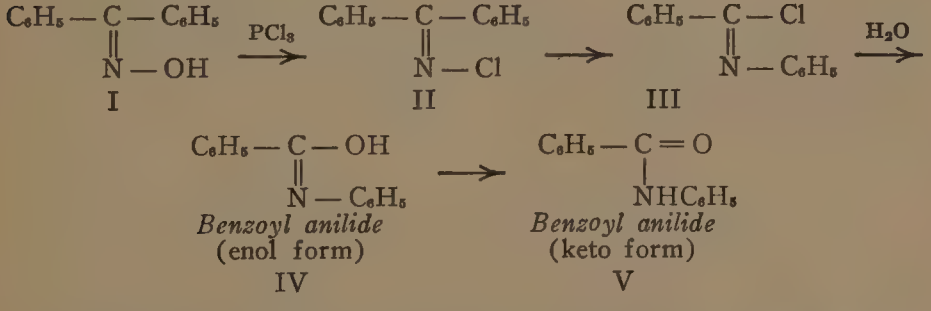
[54] Wieland, *Ber.*, **42**, 4207 (1909). *Ibid.*, **44**, 2550 (1911).
[55] Dimroth and Hartmann, *Ber.*, **40**, 4460 (1907).
[56] Petrenko-Kritschenko and Kantscheff, *Ber.*, **39**, 1452 (1906); Stewart, *J. Chem. Soc.*, **87**, 410 (1905); Acree, *Am. Chem. J.*, **39**, 300 (1908).

the oxime is formed within an hour at 100° C.[57] Side chains ortho to the carbonyl group in an aromatic ketone retard or prevent the formation of an oxime. Acetomesitylene having two side chains ortho to the carbonyl group does not form an oxime at 100° C., but when the ketone, mixed with an excess of hydroxylamine hydrochloride in absolute alcohol, is heated to 160° C. in a sealed tube, acetomesidine is formed.[58]



This is the product one would expect to obtain from the oxime through the Beckmann rearrangement.

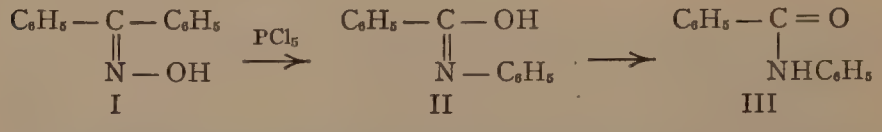
The conversion of an oxime to an amide was observed by Beckman [59] in connection with his study of benzophenone oxime. The change was accomplished first through the agency of phosphorus pentachloride, and Beckmann considered it probable that the reaction consisted of replacement of the oxime hydroxyl group by chlorine followed by a direct reaction between the halogen and one of the carbon radicals. The rearranged chlorine compound when treated with aqueous alkali was hydrolyzed to the enol form of a substituted amide and this, in turn, passed spontaneously to the isomeric keto form.



Beckmann found that other reagents could be substituted for phosphorus pentachloride. Exactly similar results were secured by treating an oxime salt with phosphorus oxychloride, phosphorus pentoxide, sulfuric acid, acetyl chloride, or with a solution of

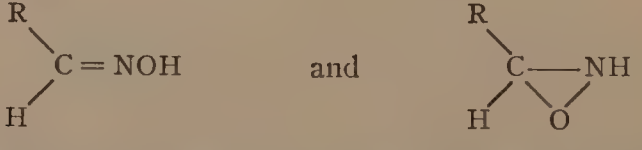
[57] Lachman obtained a good yield within five minutes by using an excess of alkali and dissolving the reagents in a mixture of alcohol and water. *J. Am. Chem. Soc.*, **47**, 260 (1925).
[58] Feith and Davies, *Ber.*, **24**, 3546 (1891).
[59] Beckmann, *Ber.*, **19**, 988 (1886).

hydrogen chloride in acetic anhydride or hydrogen chloride in glacial acetic acid.[60] It was not considered likely that compounds, analogous to the intermediate halogen derivatives II and III, were formed with all of the reagents which proved to be capable of causing the rearrangement. He therefore decided that these reagents were merely catalysts capable of establishing an environment in which a direct exchange of positions between the hydroxyl group and a carbon radical occurs spontaneously. The essential features of the mechanism as envisaged by Beckmann are represented, therefore, as follows:



The aldehydes and the unsymmetrical ketones were known to yield isomeric oximes. To account for this Hantzsch and Werner applied the principle of stereoisomerism and represented the oximes by *syn* and *anti* formulas.[61]

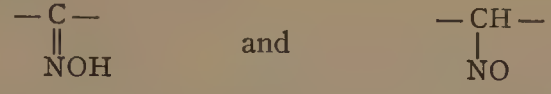
It was a logical step from this point to assume that in a Beckmann rearrangement it is the group nearest to the oxime hydroxyl group which migrates. That is to say, the radical occupying the *syn*-position with respect to the hydroxyl group is the one that exchanges places with the hydroxyl.[62] For a long time Beckmann refused to accept the view that the structures of the oximes could be determined by identifying their rearrangement products. He regarded the isomeric oximes as structurally different and wrote the formulas as follows:[63]



The structures proposed by Hantzsch and Werner are generally accepted at the present time. The only active opposition to them is found in the papers by Ponzio and his associates.[64] Ponzio believes the oximes are not geometrical isomers. To account for the

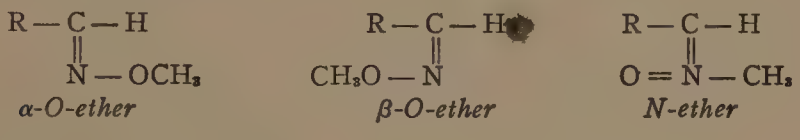
[60] Beckmann, *Ber.*, **20**, 1507, 2580 (1887); **22**, 429 (1889).
[61] Hantzsch and Werner, *Ber.*, **23**, 1243 (1890).
[62] Hantzsch, *Ber.*, **24**, 13 (1891).
[63] Beckmann, *Ber.*, **23**, 1680 (1890).
[64] Ponzio and Avagadro, *Gazz. chim. ital.*, **53**, 305 (1923); Ponzio and Ruggeri, *ibid.*, **53**, 297 (1923); Ponzio and DePaolini, *ibid.*, **56**, 274 (1926).

differences in chemical behavior he assigns different structures to the oxime group as, for example,



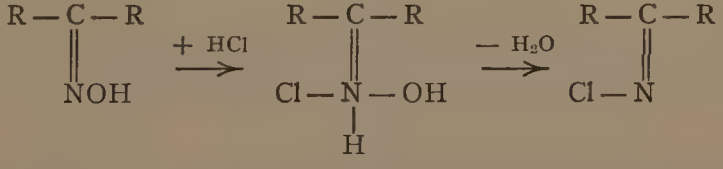
He has been able to apply this view with considerable success to the dioximes of benzil and to other dioximes, but his arguments have not been sufficiently convincing to overthrow the Hantzsch-Werner doctrine.

Ethers derived from the oximes exist in more than two forms. Methods for obtaining two O-ethers and an N-ether of an aldoxime have been developed by Brady and his associates.[65] Although two forms of N-ethers of some unsymmetrical ketoximes have been isolated and a similar isomerism is theoretically possible for the aldoximes only one N-ether has actually been prepared from any aldoxime. The known forms are written by Brady and his colleagues as follows:[66]



α-O-ether *β-O-ether* *N-ether*

Hantzsch considered the substitution of halogen for hydroxyl an essential step in the rearrangement of an oxime.[67] No modification of this view was necessary when it was shown later that it is the salt of an oxime and not the free oxime which actually changes. Dehydration of a hydrochloride would result in the formation of a chloroimido-ketone having the structure represented by formula II, page 35.



In his study of benzalacetophenone oxime, Henrich observed the formation of a white crystalline chloride when an ether solu-

[65] Brady, Dunn and Goldstein, *J. Chem. Soc.*, **129**, 2386 (1926); Brady and Bishop, *ibid.*, **127**, 1357 (1925); Brady and Goldstein, *ibid.*, **129**, 2403 (1926).

[66] Brady and Dunn, *J. Chem. Soc.*, **129**, 2411 (1926).

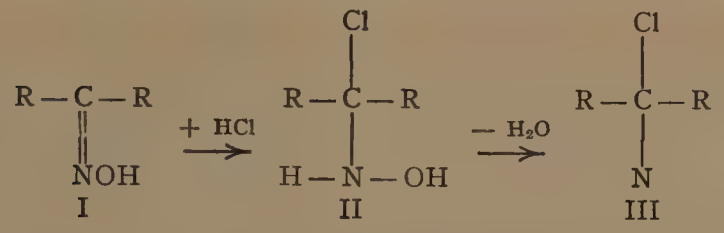
[67] Hantzsch, *Ber.*, **35**, 3579 (1902).

tion of the *syn*-oxime was treated with phosphorus pentachloride. It gradually changed to a yellow chloride. The white chloride on treatment with aqueous alkali yielded the original oxime. The yellow chloride was not stable enough to permit purification by crystallization, but, on treatment with alkali, it was converted into benzanilide.[68] The white chloride was simply the oxime salt. The yellow chloride was assumed to be a product of the rearrangement corresponding to Beckmann's formula II (page 35). The *anti*-oxime failed to rearrange under the same conditions and Henrich correlated this observation with the fact that the *syn*-compound is more basic than its isomer and, therefore, more readily forms a salt. Henrich was the first to suggest that, unless an oxime is capable of forming a salt, it is incapable of rearranging. Kuhara showed that heat alone causes the rearrangement of an oxime hydrochloride.[69] This observation was confirmed by Lehmann,[70] and a little later Lachman announced that as little as one mol of oxime hydrochloride is capable of effecting the rearrangement of twenty-five mols of free oxime when the two substances are heated to the melting point of the mixture.[71]

Stieglitz considered it probable that a chloroimido ketone was the first intermediate in the reaction, for the change is induced in an oxine salt by a dehydrating agent.[72] To test this view, a number of chloroimido esters were prepared and later the corresponding chloroimido ketones were isolated.[73] None of these compounds rearranges when warmed and some of them are stable even at 100° C. The conclusion was drawn that such a structure could not represent the very unstable intermediate that appears in the course of a Beckmann change.

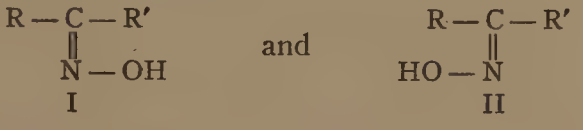
Stieglitz then suggested that the hydrogen chloride probably acts upon an oxime by addition at the double bond. Dehydration of the addition product would yield a compound of univalent nitrogen corresponding to the intermediate assumed in the Hofmann rearrangement. (See page 17.)

[68] Henrich, *Ber.*, **44**, 1533 (1911).
[69] Kuhara, Agatsuma, and Araki, *Mem. Col. Sci. Kyoto. Imp. Univ.*, **3**, 1 (1917).
[70] Lehmann, *Z. angew. Chem.*, **36**, 360 (1923).
[71] Lachman, *J. Am. Chem. Soc.*, **46**, 1480 (1924).
[72] Stieglitz and Earle, *Am. Chem. J.*, **30**, 399 (1903).
[73] Stieglitz and Peterson, *Ber.*, **43**, 782 (1910); Peterson, *Am. Chem. J.*, **46**, 325 (1911).



This assumption received strong support from Schroeter [74] but was criticized by Montagne [75] as follows:

An oxime exists in two forms,



These geometrical isomers yield different products when made to undergo the Beckmann rearrangement. Breaking the double bond in either oxime by addition of hydrochloric acid, would give rise to two stereoisomeric saturated compounds differing from each other only in the orientation of groups around the asymmetric carbon atom. The mixture of optical isomers derived from formula I would be identical with the mixture obtained from II. If the intermediates derived from the two oximes are identical, the final products must be identical, and this is contrary to our experience.

The certainty that identical mixtures of stereoisomeric salts would be formed by breaking the double bonds in the *syn* and *anti* forms of oximes, coupled with the fact that these oximes yield different rearrangement products, compelled an abandonment of this theory of addition.

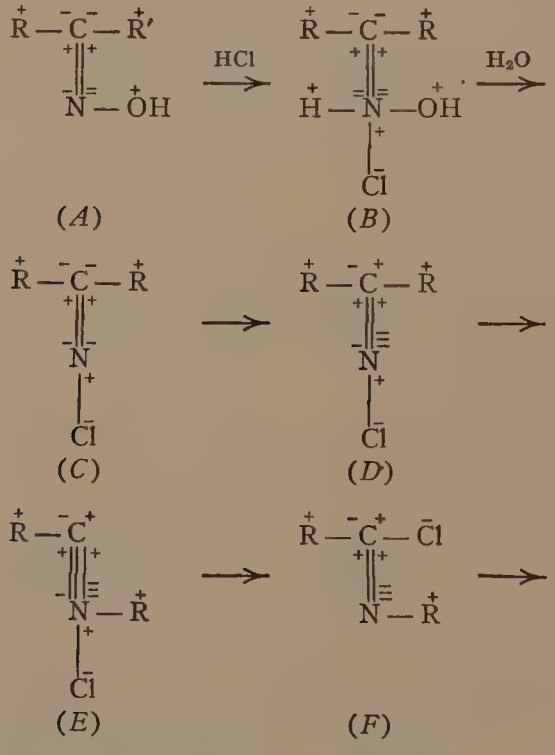
Stieglitz later revised his theory and presented a mechanism which avoids the necessity of breaking the double bond between the carbon and nitrogen. The new view has been fairly satisfactory to the majority of chemists. Only two investigators (Kuhara and Lachman) have made serious attempts to refute it.

As early as 1896, Stieglitz [76] formulated the Hofmann rearrangement of a bromoamide as due to the transient existence of an unsaturated nitrogen compound. The same principle was applied later to the Beckmann and the Curtius rearrangements, and in

[74] Schroeter, *Ber.*, **42**, 2336 (1909); *ibid.*, **42**, 3356 (1909).
[75] Montagne, *Ber.*, **43**, 2014 (1910).
[76] Stieglitz, *Am. Chem. J.*, **18**, 751 (1896).

connection with this mechanism L. W. Jones developed an electronic interpretation of the reaction.[77]

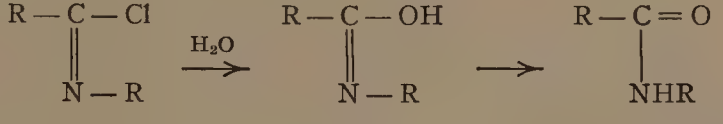
According to the mechanism proposed by Stieglitz and elaborated by Jones an oxime salt is formed by the addition of hydrogen chloride to the nitrogen atom. The hydrogen chloride is derived from the phosphorus pentachloride, phosphorus oxychloride, acetyl chloride, or other reagent used. Through loss of water, this addition product yields an unstable halogen derivative which immediately rearranges. Stieglitz now (1928) regards the change as a rearrangement of a substituted ammonium ion and he no longer uses the plus and minus signs to indicate a complete transfer of electrons from one atom to another. A valence bond is now represented as a pair of electrons shared by two atoms. A negative sign by the symbol for one atom and a positive sign by an adjacent atom means that the electron pair is closer to the electronegative atom than to the adjacent atom. For the sake of historical completeness the reaction as understood in 1914 is outlined below and



[77] Stieglitz and Slossen, *Am. Chem. J.*, **29**, 289 (1903); Stieglitz, *Ber.*, **43**, 782 (1910); Jones, *Am. Chem. J.*, **48**, 1 (1912); Jones, *ibid.*, **50**, 414 (1913); Stieglitz and Vosburg, *Ber.*, **46**, 2151 (1913); Jones, *J. Am. Chem. Soc.*, **36**, 1268 (1914); Stieglitz and Leech, *ibid.*, **36**, 272 (1914).

the language used in the explanation is that of the period when a bond was believed to be due to the complete loss of an electron by one atom and its acquisition by an adjacent atom.

The hydroxyl group in the oxime salt (*B*) is the positive radical of hydroxylamine. In order that this hydroxyl group may appear as the negative hydroxide ion of water, it must acquire two electrons from the nitrogen to which it is attached. With the loss of water, therefore, the structure (*C*) appears in which the nitrogen, $N^{\equiv}_{+}$, is in a condition virtually corresponding to the univalent nitrogen, N^{-}, of the intermediate assumed in connection with the Hofmann rearrangement. The nitrogen at once acquires two electrons from the carbon atom to which it is attached, leaving a distribution of charges as shown in (*D*). The radical, R, then migrates from Carbon, $C^{\bar{}}_{\ddagger}$, to nitrogen, $N^{\bar{}}_{\equiv}$, producing structure (*E*). By a tautomeric shift of the halogen, the stable compound (*F*) is formed. Finally, by hydrolysis, a substituted amide is obtained.

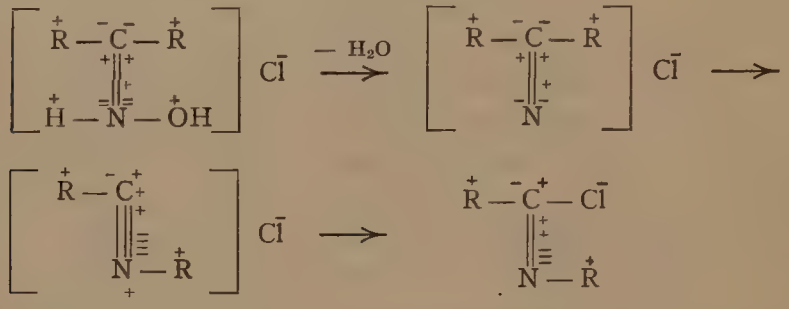


In the final product, the nitrogen, $N^{\equiv}$, is not connected with any atom that has a strong tendency to acquire electrons. In the original oxime this was not the case, for the group $\overset{+}{O}H$ is readily reduced to $\bar{O}H$. This, Stieglitz says, is the disturbing influence or the "fault" in the molecule. The reaction is initiated by the conversion of an unstable group or atom attached to nitrogen into a stable form. This is accomplished by the transfer of two electrons from the nitrogen atom, $N^{\equiv}$, causing the transient existence of a derivative of univalent nitrogen and a subsequent rearrangement which restores the nitrogen to the $N^{\equiv}$ state.

Jones states the case in a different way. He cites the fact that "in all of these types of compounds, including the monohalogen amines, the monohalogen amides and the azides, the nitrogen atom is actually or potentially in a state of oxidation corresponding to that which it has in hydroxylamine, and that it passes during rearrangement to a state of oxidation comparable to that which nitrogen has in ammonia."

Stieglitz now represents the conversion of an oxime to an

amide as a change in the configuration of the positive ion of the oxime salt. The groups within parentheses, in the formulas shown below, are the ions involved in the transformation. This scheme, with slight modification, can be applied to all of the more important rearrangements of the nitrogen compounds.

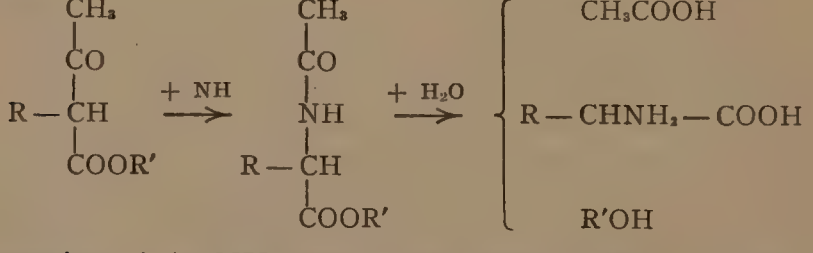


This makes the reaction a rearrangement of an ion of the ammonium type and there is ample evidence that salt formation is actually the first step in the process.

Evidence in support of the theory that univalent nitrogen radicals may exist as intermediate products has been found in other reactions. Schmidt assumes that the first step in the process of forming hydroxylamine from hydrazoic acid (azoimide) is loss of nitrogen and formation of the imine radical. The latter then combines with water.[78]

$$HN_3 \rightarrow N_2 + NH$$
$$NH + H_2O \rightarrow NH_2OH$$

The method for making α-amino acids from ketonic acids and hydrazoic acid is represented likewise as a reaction of the imine radical.



Insertion of the NH group in the carbon chain of a ketone, by treatment with hydrazoic acid, results in the formation of an acid amide. All of these syntheses are best explained under the assumption that the loss of nitrogen precedes the addition reaction.

[78] Schmidt, *Ber.*, **57**, 704 (1924).

Stieglitz regards the loss of water an essential step in the Beckmann rearrangement, and correlates this idea with the fact that the substances commonly used to induce the reaction are dehydrating agents. But on the other hand, Lachman [79] has effected the rearrangement in aqueous solution.

There is at present no agreement with respect to the importance of Lachman's observation. One of his papers when submitted for publication, was read by two referees and returned by both of them with recommendations for revision, one claimed "the assumption that the compound can be dehydrated in dilute aqueous solution is so novel that further evidence in support of the claim should be presented," the other said "there is nothing new in the idea that dehydration of such a compound can be accomplished in aqueous solution."

Lachman regards the original view of Beckmann as the best. He considers the reaction a direct interchange between the hydroxyl group and one of the carbon radicals. The function of hydrogen chloride is simply that of converting the oxime into a salt. The latter and not the free oxime is capable of rearrangement. A salt formed with a weak base, like an oxime, and a strong acid, such as hydrochloric, is very largely hydrolyzed by water. Hence, in the presence of water very little oxime salt exists. This, he thinks, accounts for the fact that dehydrating agents promote the rearrangement. It is a matter of protecting the salt from hydrolysis rather than obtaining an unstable intermediate through a forced dehydration of the salt. The condition necessary for the existence of an oxime salt in the presence of water is a high concentration of acid, and Lachman was able to accomplish the rearrangement in the presence of water when mixtures of benzophenone, hydroxylamine and hydrochloric acid were heated in sealed tubes to 150° C. for twenty hours or longer.

The claim that benzophenone oxime is rearranged by heating to 160°C. with potassium chloride and unchanged when heated with sodium chloride has not been confirmed. Lachman found that the two mixtures behave exactly alike. Both yield benzophenone and imidophenylmethane. No benzanilide is formed.

$$2\phi_2CNOH \rightarrow \phi_2CO + \phi_2CNH + (NOH)$$

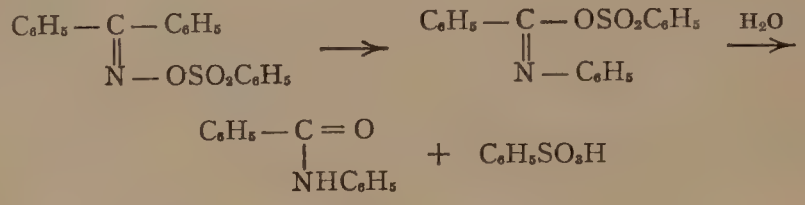
The product written (NOH) did not appear as such but as nitrogen, oxides of nitrogen, and water. The water formed reduced the yield of the imide since the latter is easily hydrolyzed.

$$\phi_2CNH + H_2O \rightarrow \phi_2CO + NH_3$$

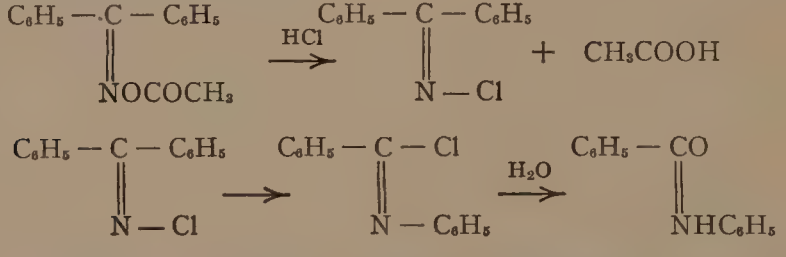
Kuhara was able to isolate the benzenesulfonic ester of benzophenone oxime from the ether solution in which it was formed.

[79] Lachman, *J. Am. Chem. Soc.*, **46**, 1477 (1924); **47**, 260 (1925).

It is a crystalline compound melting at 62° C. When warmed with an aqueous solution of potassium hydroxide it is hydrolyzed to the original oxime and potassium benzenesulfonate. When the dry crystals of the ester are heated alone above 62° C. the rearrangement occurs forming a thick yellow oil which, on hydrolysis, yields benzanilide.[80]



In cases of this kind, where the hydroxyl is replaced by a strongly negative group, Kuhara claims that salt formation is unnecessary. The ester rearranges spontaneously while the nitrogen is in the trivalent state. The corresponding acetyl derivative of the oxime requires treatment with hydrochloric acid. Kuhara assumes that the acetyl group is replaced by chloride ion and the new product rearranges through a direct reaction between the halogen and a phenyl radical.



It is difficult to reconcile Kuhara's experimental results with the univalent nitrogen theory or to claim a necessary relationship between the chemical nature of the rearranging molecule and that of the reagent that induces the change. Neither dehydration nor any other special process constitutes a necessary preliminary step according to the late Japanese investigator. The reaction goes spontaneously when a strongly negative group has replaced the oxime hydroxyl and this was the original opinion of Beckmann.[81]

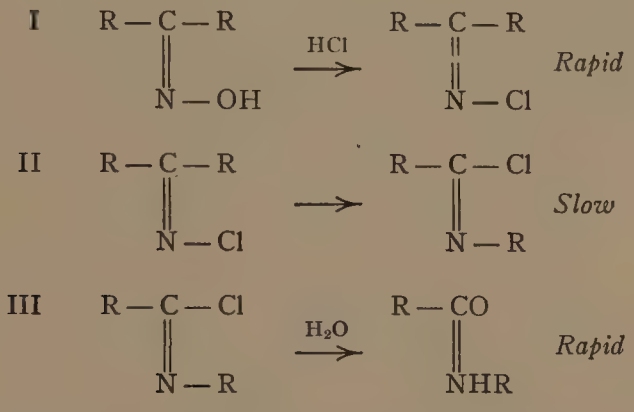
Sluiter [82] assumed the same thing in connection with his study

[80] Kuhara, Agatsuma, and Araki, *Mem. Col. Sci. Kyoto. Imp. Univ.*, **3**, 1 (1917). See also other publications in the same journal as follows: Kuhara and Okada, *ibid.*, **1**, 1 (1914); Kuhara and Suitsu, *ibid.*, **1**, 25 (1914).

[81] Beckmann, *Ber.*, **20**, 1507 (1887).

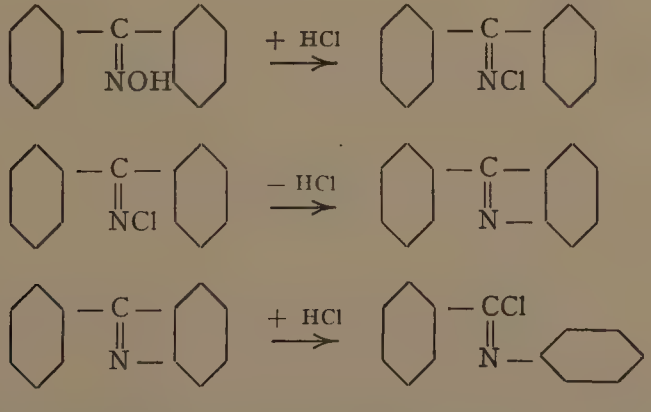
[82] Sluiter, *Rec. trav. chim.*, **24**, 372 (1905).

of the dynamics of the rearrangement of acetophenone oxime. He represents the complete reaction as a three-stage process, but, he says, only the second stage has anything to do with a molecular rearrangement and this step begins spontaneously when the oxime hydroxyl group is replaced by chlorine. The three steps are listed as follows:



The rate measured is that of the spontaneous rearrangement, II, and his data indicate that it is a unimolecular reaction.

Adopting the theory of a preliminary substitution of halogen for the oxime hydroxyl group, Wallach sought to explain the rearrangement by a mechanism that would avoid the assumption of complete dissociation of the carbon radical in its passage from carbon to nitrogen.[83] Taking benzophenone oxime as an example he outlined the course as follows:

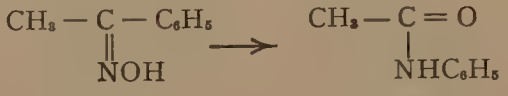


Montagne pointed out that Wallach's theory is untenable since it involves attachment of the benzene nucleus to nitrogen at a

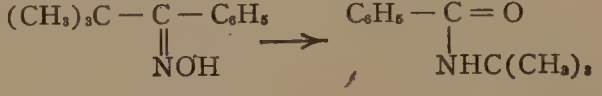
[83] Wallach, *Ann.*, **346**, 266 (1906).

different position in the ring than the original position of attachment to carbon.[84] Rearrangements involving the migration of *ortho* and *para* substituted rings indicate that in the final product connection is made with nitrogen through the same bond that originally attached the radical to carbon.[85]

Only one member of the possible pair of isomers is obtained when a mixed aliphatic-aromatic oxime is prepared. It is usually the aromatic radical that migrates to the nitrogen atom when such an oxime is treated with the Beckmann reagents. Thus acetophenone oxime is converted into acetanilide.



There are a few exceptions to this rule. It is reported that pivalophenone oxime when warmed with phosphorus pentachloride yields benzoyltertiarybutyl amine through migration of the alkyl radical.[86]

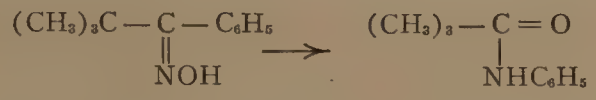


When an acetic acid solution of the oxime is saturated with hydrogen chloride and boiled for two hours under a reflux condenser pivalic anilide is formed through migration of the phenyl group.

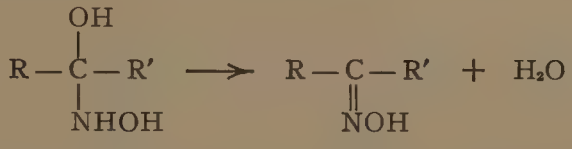
[84] Montagne, *Rec. trav. chim.*, **25**, 376 (1906).

[85] The same thing applies to the pinacol and to the benzil rearrangements. When 4,4′-dimethylbenzophenone oxime is subjected to the Beckmann rearrangement and the product is hydrolyzed, *para*-toluic acid and *para*-toluidine are formed. Goldschmidt, *Ber.*, **23**, 2746 (1890); Montagne, *ibid.*, **51**, 1479 (1918), 4,4′-dichlorohydrobenzoin yields 4,4′-dichlorodiphenylacetaldehyde. Montagne, *Rec. trav. chim.*, **21**, 30 (1902). 4,4′-dichlorobenzil yields 4,4′-dichlorobenzilic acid. Montagne, *Rec. trav. chim*, **21**, 6 (1902). *Ortho*-nitrobenzbromamide yields *ortho*-nitroaniline, Stieglitz, *Am. Chem. J.*, **29**, 58 (1903); Weerman, *Rec. trav. chim.*, **26**, 203 (1907), and *para*-substituted pinacols yield *para*-substituted pinacolones. Montagne and Koopal, *Rec. trav. chim.*, **29**, 136 (1910). For an exception to this rule see Claisen and Tietze, *Ber.*, **59**, 2344 (1926).

[86] Schroeter, *Ber.*, **44**, 1201 (1911). The products actually isolated from the oxime when treated with phosphorus pentachloride were benzonitrile and tertiarybutyl chloride. Schroeter claims that this result indicates the preliminary shift of the tertiarybutyl group to nitrogen for benzoyltertiarybutylamine prepared from benzoyl chloride, and tertiarybutylamine decomposes when warmed with phosphorus pentachloride, yielding the same products. It is obvious that this process of reasoning by analogy is not safe. It would be just as sound to assume that phosphorus pentachloride ruptures this oxime without rearrangement, whereas the milder reagent causes the usual change.



The failure to obtain both forms of a ketoxime when the radicals attached to the carbonyl group are quite different in character led Hantzsch to assume that in oxime formation the hydroxyl group is definitely oriented by attractive forces exerted by the ketone radicals. Elaborating this idea Meisenheimer and his colleagues assume that an intermediate addition product is formed between the ketone and hydroxylamine.[87] The addition product then decomposes into an oxime and water.



In connection with this mechanism they say the attraction, or a corresponding repulsion between the groups, may be strong enough to prevent free rotation around the C—N axis and the intermediate may, on that account, be compelled to lose water in only one way, the formation of one member of the pair of stereoisomeric oximes being thereby excluded.

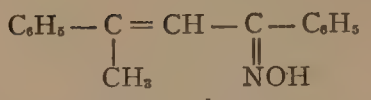
Arranged in the order of their tendency to be oriented by an attraction of the hydroxyl group, Hantzsch prepared the following list:

1. $-CH_2COOH$
2. $-CH_2CH_2COOH$
3. $-COOH$
4. $-C_6H_5$
5. $-C_6H_4X$ (meta or para)
6. $-COC_6H_5$
7. $-C_6H_4X$ (ortho)
8. $-C_3H_4S$ (thienyl, the thiophene residue)
9. $-C_nH_{2n}+1$ $(n > 1)$
10. $-CH_3$

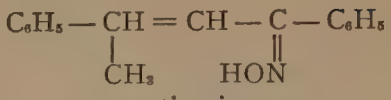
Hydrogen was not included in the list. It probably should be placed near the phenyl radical for benzaldoxime exists in stereoisomeric forms.

When the isomeric forms of oximes are stable enough to permit isolation there is often considerable difference in their tendencies to rearrange. Henrich [88] prepared the two oximes of dypnone and assigned to them the following structures.

[87] Meisenheimer, Lange and Lamparter, *Ann.*, **444**, 94 (1925).
[88] Henrich, *Ber.*, **44**, 1533 (1911).

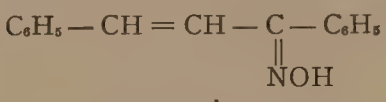


syn-oxime
labile, m.p. 134°C.

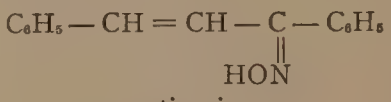


anti-oxime
stable, m.p. 78°C.

He prepared also the oximes of benzalacetopheonone and ascribed to them the following configurations:

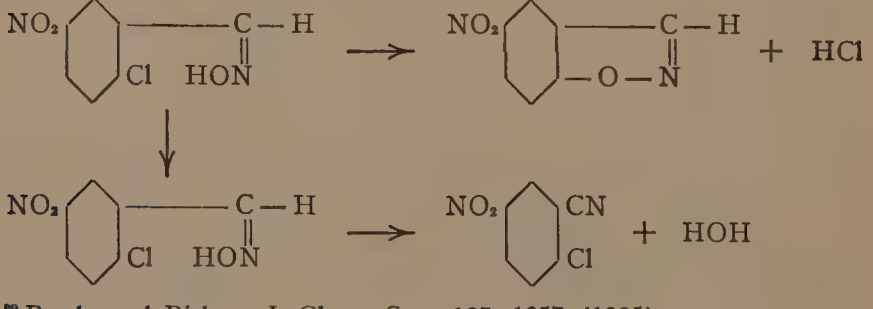


syn-oxime
unstable, m.p. 116°C.



anti-oxime
stable, m.p. 75°C.

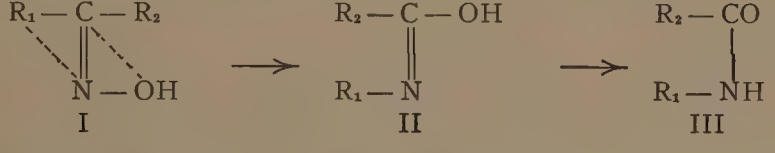
Of these two pairs of oximes, only the *syn*-modifications can be rearranged by the usual methods. The rearrangement is most successful when phosphorus pentachloride is used. As stated earlier, Hantzsch assumed that the rearrangement always occurs between groups on the same side of the molecule. This theory has been generally accepted and since 1891 structural formulas have been assigned to ketoximes on the basis of the products formed through the Beckmann rearrangement. For the configurations of the aldoximes we have depended primarily upon the fact that the acetyl derivative of one member of the pair of geometrical isomers when warmed with an alkali readily lose acetic acid giving rise to a nitrile, whereas, the acetyl derivative of the other is hydrolyzed to the original oxime. Assuming that elimination of acetic acid can occur when the hydrogen atom and the acetyl group are on the same side of the molecule, but not otherwise, we have a means of determining the orientation of radicals in aldoximes. As a matter of fact, this method is quite unreliable. Brady and Bishop prepared the two forms of 2-chloro-5-nitrobenzaldoxime and found that the one which readily forms the nitrile by loss of water is also the one which forms an isoxazole by loss of hydrogen chloride.[89]



[89] Brady and Bishop, *J. Chem. Soc.*, **127**, 1357 (1925).

The formation of an anhydride from an *amphi*-glyoxime is another example of *trans*-elimination. The *syn* form of cinnamaldoxime is converted into the benzoyl derivative of the *anti* modification during the process of treatment with benzoyl chloride.[90] Many other recent experiments have shown an easy conversion of one form of an oxime into a derivative of the other by a *trans*-addition, *trans*-elimination, or a *trans*-interchange.[91]

Meisenheimer believes that the Beckmann rearrangement of oximes involves an exchange of places "not between the neighboring groups, but between the groups in the anti-positions." [92] If this be true every oxime whose structure has been determined by reference to the rearrangement products must hereafter be written in the reverse form. Bucherer was probably the first to suggest that the groups on opposite sides of the molecule exchange places.[93] In an attempt to avoid the idea of a temporary dissociation of the molecule Bucherer assumed the existence of secondary or partial valence bonds as indicated by dotted lines in formula I.

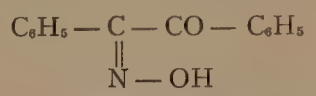


In a medium that promotes rearrangement the partial valences become stronger and the primary bonds weaker until an actual reversal is accomplished. This view has been supported by others.[94] A recent attempt has been made to use Perrin's concept of semivalence or single electron bonds to explain the formation of intermediate products in a great variety of reactions.[95]

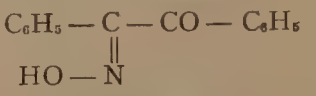
Meisenheimer observed that triphenylisoxazol, on oxidation, yields a benzoyl derivative of γ-benzil monoxime.[96] The γ-benzil

[90] Brady and Thomas, *J. Chem. Soc.*, **121**, 2098 (1922).
[91] Beckmann, Liesche, and Correns, *Ber.*, **56**, 341 (1923); Auwers and Ottens, *Ber.*, **57**, 446 (1924); Brady and Grayson, *J. Chem. Soc.*, **125**, 1418 (1924); Brady and Bishop, *ibid.*, **127**, 1357 (1925).
[92] Meisenheimer, *Ber.*, **54**, 3206 (1921).
[93] Bucherer, "Lehrbuch der Farbenchemie," **1914.**
[94] Biltz and Robl, *Ber.*, **54**, 2441 (1921).
[95] Mme. Ramart-Lucas, *Compt. rend.*, **185**, 561, 718 (1927).
[96] For the preparation and properties of isoxazols see Meisenheimer and Weibzahn, *Ber.*, **54**, 3195 (1921); Knovenagel and Walter, *Ber.*, **37**, 4502 (1902).

monoxime is now regarded as the *syn*-phenyl compound.[97] The two isomers are represented by the following formulas:

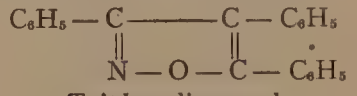


α-Benzil monoxime

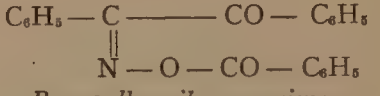


γ-Benzil monoxime

The triphenylisoxazol and its oxidation product are represented by the following structures:



Triphenylisoxazol

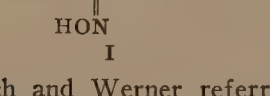


Benzoylbenzil monoxime

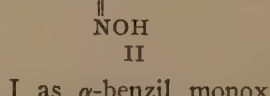
Since both carbonyl groups in this benzoylbenzil monoxime are produced by the breaking of an ethylene double bond, they must be on the same side of the molecule, i.e. in *cis* positions. This oxidation product must be the benzoyl derivative of that particular benzil oxime which contains the oxime hydroxyl and the benzoyl radical on the same side of the molecule. Yet it rearranges to a substituted amide in which the phenyl group is found attached to nitrogen.

On account of the fundamental importance of the Beckmann rearrangement in the determination of the configuration of oximes, it was important to prove that the benzoylbenzil oxime obtained was actually the primary product of the oxidation and not a secondary product obtained by rearrangement. The triphenylisoxazol was first oxidized with chromic acid in boiling glacial acetic acid solution. Under these conditions, rearrangement was possible. Oxidation by ozone was considered safer. Ozonization was carried out in cold carbon tetrachloride solution and decomposition of the

[97] There is some confusion in the literature in the nomenclature of benzil oximes. The monoximes are represented by the following structures:



I



II

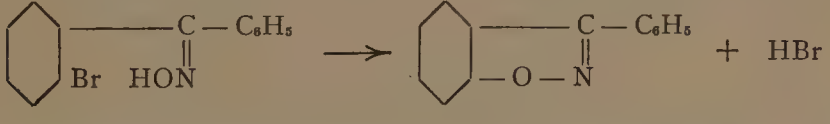
Hantzsch and Werner referred to formula I as α-benzil monoxime and II as the γ-oxime. Hantzsch and Werner, *Ber.*, **23**, 11 (1890). The names were assigned on the basis of supposed structural relationships between these compounds and the benzil dioximes. Beckmann and Köster reversed these names, or the structures to which the old names applied, for they obtained products from the α-oxime corresponding to products which should come from the compound then known as the γ-oxime. Beckmann and Köster, *Ann.*, **274**, 1 (1893). See also Werner and Piguet, *Ber.*, **37**, 4295 (1904).

ozonide was accomplished by treatment with cold water. Here a rearrangement would not be expected, but there was no definite proof that it was excluded. The possibility of obtaining the benzoyl derivative of the γ-oxime when the α-oxime is treated with benzoyl chloride was considered. The conclusion that no such change accompanies benzoylation rests upon the fact that upon saponification of benzoyl-γ-benzil oxime, the original unchanged oxime is recovered, and the acetyl derivative of the α-monoxime likewise hydrolyzes to the original oxime.[98] But, unfortunately, attempts to prepare the benzoyl derivative of the α-monoxime failed. A compound was obtained which, on hydrolysis with sodium hydroxide, yielded benzonitrile and benzoic acid. For a time it was assumed to be a dibenzoyl derivative of isobenzamide.[99]

$$C_6H_5-C(=N-CO-C_6H_5)-O-CO-C_6H_5$$

It was thought that a Beckmann rearrangement had occurred during the process of benzoylation. This was refuted later by Meisenheimer and Lamparter who showed that the benzoylation is normal, but rearrangement occurs during the subsequent treatment with alkali.[100] This leaves an element of uncertainty in the problem.

Attempts have been made to verify the assumption that *anti* groups take part in the Beckmann rearrangement by using oximes whose structures could be determined without resort to such preliminary reactions as were used in breaking the ring of an isoxazol. For example, *ortho*-bromobenzophenone oxime yields hydrobromic acid when warmed with concentrated sodium hydroxide solution. The easy removal of the halogen acid suggests the *syn* structure.



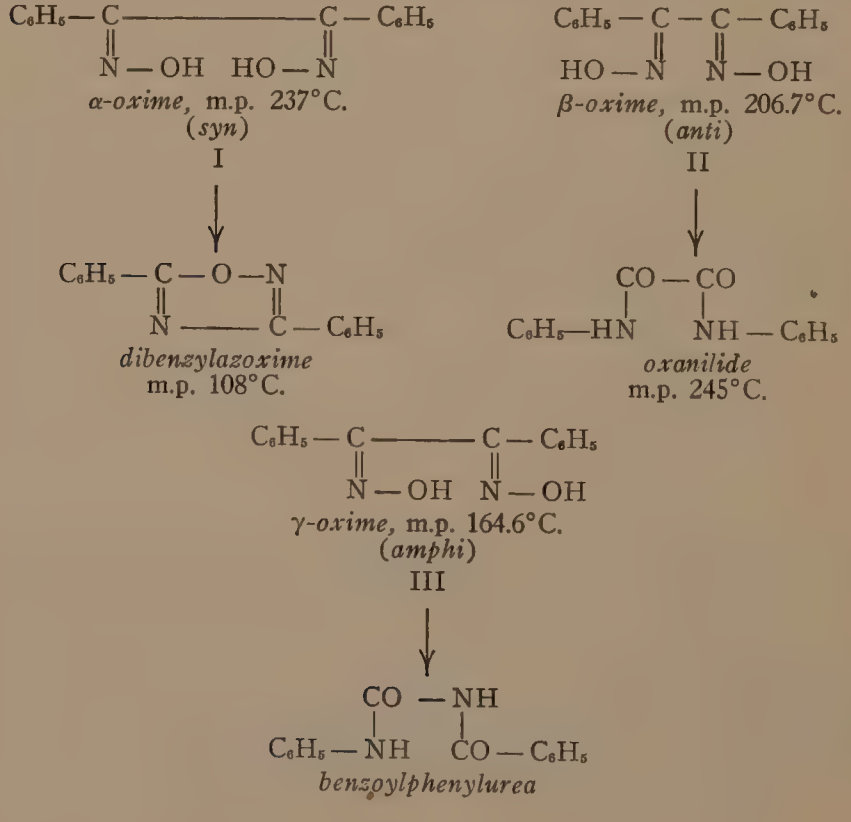
Treatment with phosphorus pentachloride converts the oxime into an anilide of *ortho*-bromobenzoic acid. No bromoanilide of benzoic acid is formed.[101] The result would be more convincing if a form

[98] Beckmann and Sandel, *Ann.*, **296**, 279 (1897); Auwers and Meyer, *Ber.*, **22**, 537 (1889).
[99] Werner and Piguet, *Ber.*, **37**, 4295 (1904); Meisenheimer, *Ber.*, **54**, 3206 (1921).
[100] Meisenheimer and Lamparter, *Ber.*, **57**, 276 (1924).
[101] Meisenheimer and Meis, *Ber.*, **57**, 289 (1924).

of this oxime could be made which does not yield hydrogen bromide upon treatment with alkali. The isomeric form (presumably the *anti*-form) of the oxime has not been prepared.

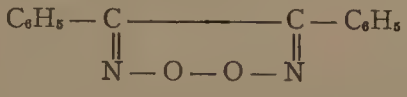
Statements to the effect that Meisenheimer's work has overthrown the earlier views relating to oxime rearrangements are premature. His work has, however, made it highly desirable to obtain new evidence relating to oxime structures. The old theory of *cis*-migration has been weakened. The new theory of *trans*-interchange has not been established. That the same form of an oxime may rearrange one way under certain conditions and in the opposite way in a different environment is a possibility to be considered.

If we adopt the reversed configurations for the monoximes we must make corresponding changes in the structural formulas of the dioximes. The formulas that we have, in the past, assigned to the benzil dioximes were based upon the assumption that the groups which take part in a Beckmann transformation are on the same side of the molecule. From these relations we have the following:

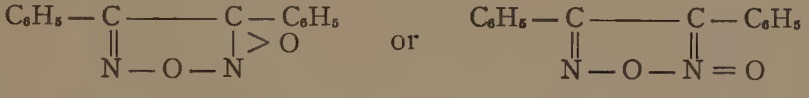


There has always been some uncertainty about the dioxime structures for other reactions have not always corroborated the conclusions drawn from the Beckmann reaction. For example, the γ-oxime forms a diacetyl derivative which upon saponification yields an oxime anhydride, diphenylfurazan. From this reaction we would suppose that the hydroxyl groups are in the *syn* position. The *syn* structure was originally assigned to the γ-oxime on this account.[102] The free γ-dioxime has the same tendency to form the anhydride.

The *syn* formula for the γ-dioxime is supported also by the observation that diphenylgloxime peroxide on reduction yields the γ-dioxime.[103] The peroxide is said to have the formula



This structure of the peroxide, however, has not been established with certainty.[104] It may be



An argument in support of the *amphi* structure for the γ-oxime is found in the fact that it yields benzoylphenylurea when subjected to the rearrangement. This is the only one of the three dioximes to which the same structure would be assigned under the old and the new views concerning the groups that take part in the Beckmann reaction. Benzoylphenylurea would come from the *amphi* structure whether it is the *cis* or the *trans* groups that exchange places.

In order to obtain this product from an oxime having the *syn* structure it would be necessary for one of the oxime hydroxyl groups to react with a phenyl group in the *cis* position and for the other to exchange places with a phenyl group in the *trans* position. Although this would be an unexpected result it is a possibility that must not be ignored.

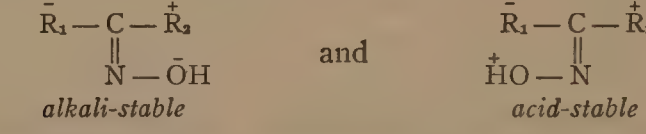
The isomeric oximes differ in their stabilities in acids and in alkalies. Abegg assumes that the electrochemical character of the

[102] Hantzsch and Werner, *Ber.*, **23**, 11 (1891); Auwers and Meyer, *Ber.*, **21**, 784 (1888); **22**, 705 (1889); Beckmann and Koster, *Ann.*, **274**, 25, 34 (1893).

[103] Angeli, *Ber.*, **25**, 1956 (1892).

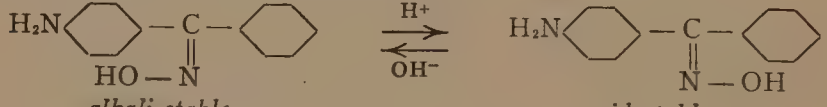
[104] Wieland and Senper, *Ann.*, **358**, 36 (1908).

oxime hydroxyl changes with the environment, being more negative in an alkaline than in an acid medium.[105] The terms positive and negative and the plus and minus signs used in this connection represent only slight differences in electrochemical character and not actual polarity. If R_1 is negative with respect to R_2 then the isomeric oximes—according to Abegg—have the configurations



In support of the new conception of the rearrangement, viz., that groups in *trans* positions migrate, it has been pointed out that when alkali-stable oximes undergo the rearrangement it is the more strongly negative group that migrates and when acid-stable oximes rearrange it is the more positive group that shifts.[106] The rearrangement, however, is accomplished in an acid medium and there is the possibility of isomerization of the oxime in advance of rearrangement.

If there is considerable difference in the electrochemical natures of the carbon radicals of a ketone the alkali-stable form may be the only one having sufficient stability to permit isolation. Thus the only known oxime of acetophenone is the one in which the phenyl group migrates. In many cases, where the two stereoisomeric oximes are known, a conversion of one into the other can be made by changing the environment. The oximes of *ortho*-aminobenzophenone afford an example.



alkali-stable
m.p. 156°C.
(h-oxime)

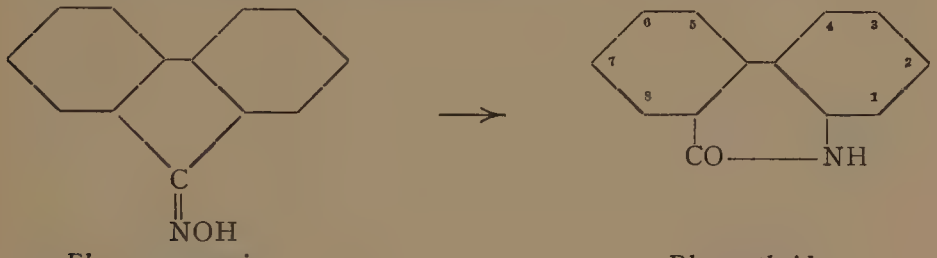
acid-stable
m.p. 127°C.
(n-oxime)

These oximes have been studied with the hope of finding positive evidence for or against Meisenheimer's theory. Through the action of dehydrating agents water is eliminated between the hydroxyl and amino groups. The ring compound formed is phenyl indazole. It was thought that this reaction could be used to determine in which of the two oximes the hydroxyl and amino group

[105] Abegg, *Ber.*, **32**, 291 (1899).
[106] Beckmann, Liesche and Correns, *Ber.*, **56**, 341 (1923).

are on the same side of the molecule. But the same indazole was obtained from either oxime.[107] One of them isomerizes in advance of the dehydration or else water can be eliminated from either form of the oxime.

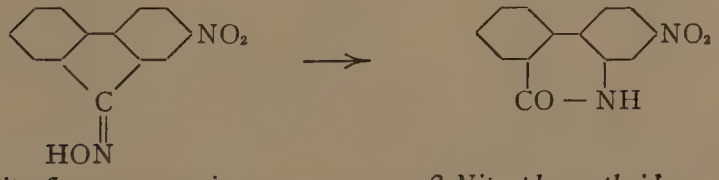
Beckmann and Wegerhoff obtained a reaction between fluorenone oxime and phosphorus pentachloride but were unable to identify the product.[108] The experiment has been repeated recently and the product identified as phenanthridone.[109]



Fluorenone oxime *Phenanthridone*

Isomeric unsymmetrical derivatives of fluorenone oxime responding to the Beckmann change, should yield different phenanthridones. Moore and Huntress applied this idea in an attempt to confirm or refute Meisenheimer's theory that *trans*-interchange occurs. Assuming *trans*-interchange the results would be as follows:

2-Nitrofluorenone oxime (syn) *7-Nitrophenanthridone*

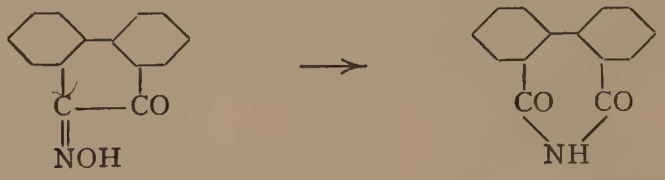


2-Nitrofluorenone oxime (anti) *2-Nitrophenanthridone*

Only one oxime could be obtained. The result, therefore, is inconclusive. The product formed, on treatment with phosphorus pentachloride, yielded exclusively 7-nitrophenanthridone.

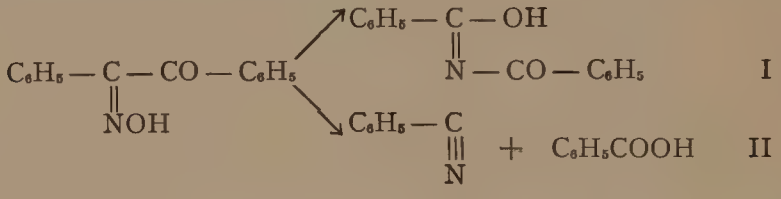
[107] Auwers and Jordan, *Ber.*, **57**, 800 (1924).
[108] Beckmann and Wegerhoff, *Ann.*, **252**, 35 (1889).
[109] Moore and Huntress, *J. Am. Chem. Soc.*, **49**, 2618 (1927).

In all cyclic ketoximes the normal Beckmann rearrangement results in an expansion of the ring. The six-membered ring of phenanthraquinone oxime, when warmed with acetic anhydride and hydrogen chloride, is converted into the seven-membered ring of a diphenimide.



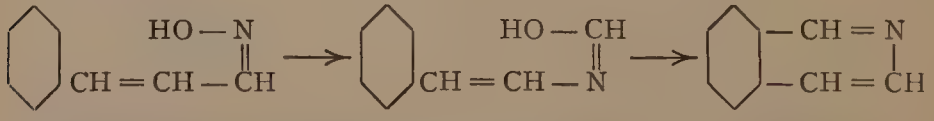
On the other hand when this oxime is warmed with benzenesulfonyl chloride in pyridine solution it yields a nitrile.[110]

Similarly α-benzil monoxime, when treated with benzenesulfonyl chloride, yields two products.[111]



Reaction II predominates when the reagents are dissolved in pyridine.

Among the applications of the Beckmann reaction in synthetic lines the preparation of *iso*quinoline from cinnamic aldoxime is of interest.[112]



The oxime of cyclopentanone is converted into piperidone [113] and *iso*nitrosocamphor into camphorimide.[114]

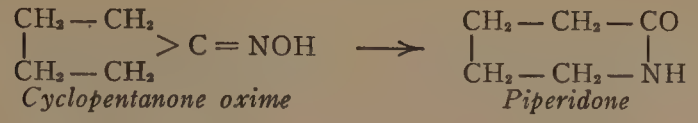
[110] Beckmann and Wegerhoff, *Ann.*, **252**, 1 (1899); Beckmann and Liesche, *Ber.*, **56**, 1 (1923).

[111] Werner and Piguet, *Ber.*, **37**, 4295 (1904). For a discussion of diacetyl oximes see Diels and Stern, *Ber.*, **40**, 1622 (1907).

[112] Bamberger and Goldschmidt, *Ber.*, **27**, 1954 (1894).

[113] Wallach, *Ann.*, **312**, 171 (1900); **346**, 266 (1906).

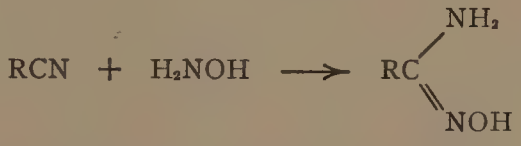
[114] Angeli, *Atti. accad. Lincei* [5], **1**, 441 (1892).



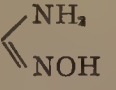
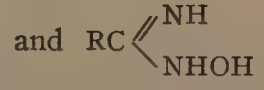
Cyclopentanone oxime *Piperidone*

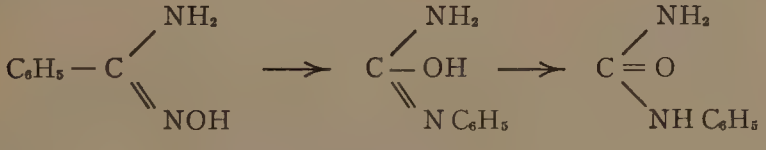
An analogy exists between the behavior of ketoximes and ketodiazides.[115] This is shown by the work of Forster,[116] Schroeter [117] and others. The reactions have been reviewed in connection with the azides. (See page 26.)

Amidoximes. The aliphatic amidoximes are obtained by the action of hydroxylamine on nitriles.[118]



Aromatic amide oximes are usually made from thioamides by treatment with hydroxylamine.

Of the two structures,  and  the former accounts best for most of the amidoxime reactions. They are easily hydrolyzed to the corresponding amide and hydroxylamine. With nitrous acid they yield amides, nitrous oxide and water. They undergo the Beckmann rearrangement yielding substituted ureas. Benzenesulfonyl chloride converts benzamidoxime into phenyl urea.



[115] Schroeter, *Ber.*, **42**, 2336, 3356 (1909).
[116] Forster, *J. Chem. Soc.*, **95**, 184 (1909).
[117] Schroeter, *Ber.*, **44**, 1201 (1911).
[118] Tiemann, *Ber.*, **22**, 2391 (1889).

Chapter II

Migrations from Nitrogen to Carbon.

ALKYLAMINOBENZENES

The first example of a molecular rearrangement involving the shift of a carbon radical from amino nitrogen to the para position in the benzene ring was discovered by A. W. Hofmann. In the preparation of methyl aniline from methyl alcohol and aniline hydrochloride, Hofmann and Martius [1] observed that dimethyltoluidine and dimethylxylidine appeared as by-products. They assumed that complete methylation of the amino group was first accomplished and that this result was followed by a migration of a methyl radical from nitrogen to the ring. That is to say, they regarded the rearrangement as a reaction of a quaternary ammonium compound.

Hofmann [2] investigated the effect of heat and pressure upon pure trimethylphenylammonium iodide and found that methylation in the ring is accomplished progressively as indicated by the following equations:

$$C_6H_5N(CH_3)_3I \longrightarrow CH_3C_6H_4N(CH_3)_2HI \longrightarrow$$
$$(CH_3)_2C_6H_3NH(CH_3)HI \longrightarrow (CH_3)_3C_6H_2NH_2HI$$

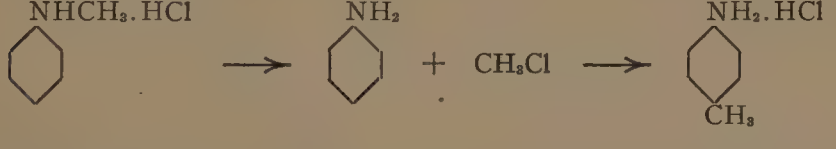
The quaternary compound is stable at 200° C. At 250° C. to 280° C. the reaction is slow and the products are principally dimethyltoluidine and methylxylidine. At 335° C. the chief product due to rearrangement is the primary aromatic amine, mesidine.

Extending his investigation to homologues of methylaniline Hofmann [3] found that ethyl, amyl and other alkyl radicals migrate from nitrogen to the carbon nucleus whenever the halogen acid salt of an alkylated aromatic amine is heated for several

[1] A. W. Hofmann and C. A. Martius, *Ber.*, **4**, 742 (1871). Ten kg. of crystallized aniline hydrochloride and six kg. of methyl alcohol were heated to 280°C.-300°C. for eight or ten hours in an autoclave.
[2] Hofmann, *Ber.*, **5**, 704, 720 (1872).
[3] Hofmann, *Ber.*, **7**, 526 (1874).

hours in a sealed tube. If the temperature is maintained above 300° C. the principal product is a primary amine. At lower temperatures secondary and tertiary amines predominate, alkyl radicals remaining attached to nitrogen. When ethyl aniline was heated for twelve hours at 300° C. to 330° C. at least three products of rearrangement were found. The main part of the mixture distilled between 212° C. and 216° C. and formed a platinum salt corresponding to the formula, $C_2H_5C_6H_4NH_2.HCl.PtCl_4$. The by-products were identified as compounds in which two or more ethyl groups had entered the benzene ring.

Many applications of this rearrangement have been made and a great variety of opinions have been expressed concerning its mechanism.[4] Although quaternary ammonium compounds may be formed at temperatures below that required for rearrangement there is evidence that at higher temperatures the salts of tertiary and of secondary nitrogen bases undergo the same change. A possible course of the reaction is a dissociation of the salt of the alkylated amine with the formation of an alkyl halide which, under the conditions of the experiment, reacts with hydrogen of the aromatic nucleus, forming hydrogen halide and an alkyl substituted ring. The conversion of methyl aniline into *para*-toluidine, according to this scheme, is accomplished as follows:



Michael outlined this mechanism of the reaction soon after its discovery. Many years later he restated his opinion in these words:

"Rearrangements are frequently assumed to take place with substances that are in themselves either perfectly stable, or, when heated sufficiently, decompose in an entirely different manner. It is certainly remarkable that so many typical rearrangements should still be theoretically misinterpreted in this way, as, for instance, with the transformation at a high temperature, of methylaniline-iodo- and chlorohydrate into the corresponding salts of *o*- and *p*-toluidine, respectively. In this case, the so self-evident explanation has been known for many years (Michael, *Ber.*, **14**, 2107 (1881)) i.e., that the isomerization must take place through the dissociation of the salts into aniline and methyl halide. They can now only react differently on each other, as they can not reunite under the prevailing condition of temperature,

[4] Benz, *Ber.*, **15**, 1646 (1882); Hofmann, *Ber.*, **18**, 1821 (1885); Nölting and Baumann, *Ber.*, **18**, 1150 (1885); Nölting and Forel, *Ber.*, **18**, 2681 (1885); Limpach, *Ber.*, **21**, 640 (1888); Hodgkinson and Limpach, *J. Chem. Soc.*, **61**, 420 (1892). Reilly and Hickinbottom, *ibid.*, **117**, 103 (1920).

the halogen atoms attacking the easily replaceable hydrogen in the aromatic nucleus of the base with the formation of salts of the more strongly basic toluidines." [5]

According to Howard and Derick no rearrangement of methylaniline hydrochloride occurs below 250° C.[6] They assume that at temperatures between 200° C. and 250° C. methyl chloride dissociates from one molecule of the amine salt and reacts with the amino group of another until trimethylphenylammonium chloride is formed. An equilibrium exists between the salts of the resulting primary, secondary and tertiary amines and the quaternary compound. At a higher temperature the equilibrium is disturbed by the irreversible rearrangements of the quaternary compound. The rearrangement is caused by dissociation of methyl chloride as indicated above, according to these investigators, but only from the quaternary ammonium salt. This assumption—the original Hofmann idea—puts the reaction in harmony with Derick's [7] theory that rearrangement occurs only when there exists the possibility of forming an isomeric compound having a much lower ionization constant. As bases the toluidines and methylanilines have approximately the same strength. But the difference in basicity between toluidine and trimethylphenylammonium hydroxide is enormous. According to Derick it is only when the quaternary derivative is formed that the difference in basicity is sufficient to render the compound unstable.

CONSTANTS OF METHYLANILINES AND TOLUIDINES.[8]

Substance	K_b	Temperature, °C.
Methylaniline	2.55×10^{-10}	18
Dimethylaniline	2.42×10^{-10}	18
Trimethylphenyl-ammonium hydroxide	1.0	18
p-Toluidine	1.6×10^{-9}	18
o-Toluidine	3.0×10^{-10}	18
m-Toluidine	3.9×10^{-10}	15
Dimethyl-*o*-toluidine	3.08×10^{-9}	15
Dimethyl-*m*-toluidine	2.4×10^{-9}	25
Dimethyl-*p*-toluidine	6.36×10^{-9}	15

The free energies of formation of isomeric compounds would be more fundamental criteria of relative stabilities and of the

[5] Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920).
[6] For the preparation of mesidine see Porter and Thurber, *J. Am. Chem. Soc.*, **43**, 1194 (1921).
[7] Derick and Bornmann, *J. Am. Chem. Soc.*, **35**, 1269 (1913).
[8] Howard and Derick, *J. Am. Chem. Soc.*, **46**, 167 (1924).

possibilities of rearrangement. Unfortunately we have no accurate free energy data relating to these compounds. Heats of combustion have been measured with sufficient accuracy to afford a basis of predictions in some cases.[9]

Free methylaniline is not changed to toluidine by heat alone, but in the presence of metallic salts such as cobalt chloride, cadmium chloride or manganese chloride the secondary amine undergoes the rearrangement in the normal way.[10] The presence of the salt insures the formation of a compound of pentavalent nitrogen. Rearrangement occurs only when the nitrogen is in this state. The fact that a negative radical, X, must be present lends support to the theory that the alkyl group, R, leaves the nitrogen as RX. The dissociation of RX from $C_6H_5NHR.HX$, at an elevated temperature, would produce such compounds as $C_6H_5NH_2$, C_6H_5NHR, $C_6H_5NR_2$ and $C_6H_5NR_3X$. These compounds have been isolated as decomposition products of methylaniline hydrochloride when the salt was heated for several hours in a sealed tube at 200° C.-250° C.[11] or for a shorter time at 310° C.[12]

On this account Beckmann and Correns think the reaction should not be classified as a rearrangement. But if we drop from this category all cases that are believed to be due to two or more distinct processes in which there is temporarily a separation of component parts of the molecule the term rearrangement will apply only to very obscure processes of isomerization. Even in this case the mechanism is not definitely established. Michael's claim has received substantial support in the observations of many competent investigators, but there are equally valid arguments against it.

If the alkyl amine salt dissociates into an alkyl halide and the free amine and these later take part in an ordinary metathesis, then any procedure which favors the escape of the amine or the alkyl halide should reduce the yield of the substitution product. To apply this test Hickinbottom [13] heated pure ethylaniline with cobalt chloride in a long vertical glass tube. The mixture was heated to 240° C-270° C. for twelve hours. The lower part of the tube was always at a temperature above the boiling point of aniline and

[9] Roth and Stoermer, *Ber.*, **46**, 260 (1913).
[10] Reilly and Hickinbottom, *J. Chem. Soc.*, **117**, 103 (1920).
[11] Howard and Derick, *J. Am. Chem. Soc.*, **46**, 166 (1924).
[12] Beckmann and Correns, *Ber.*, **55**, 852 (1922).
[13] Hickinbottom, *J. Chem. Soc.*, **130**, 64 (1927).

the apparatus was arranged so as to permit the collection of volatile products at any time. The rearrangement proceeded smoothly but no ethyl chloride was detected and the yield of aniline was negligible. Similar results were obtained with *n*-butylaniline. During fifteen hours of heating at 230° C.-240° C. no free aniline nor butylchloride appeared. That cadmium, cobalt and manganese chlorides do not accelerate the reaction between alkyl halides and the benzene ring had been established previously. The absence of moisture did not alter the result. Ethyl aniline dried over fused potassium hydroxide or phosphorus pentoxide was distilled onto anhydrous cobalt chloride in a tube which was open to the air only through a train of phosphorus pentoxide drying towers. When heated the rearrangement occurred as in the earlier experiments.

When ethylaniline hydrochloride was heated in an open tube free aniline was obtained. Butylaniline hydrochloride under the same treatment was converted into the primary amine, *para*-amino-*n*-butylbenzene if the salt were not contaminated with a volatile impurity. In the presence of free hydrogen chloride or of benzene, *n*-butyl chloride and aniline were isolated.

From the results obtained by Hickinbottom one must conclude that actual dissociation is not a necessary antecedent to the rearrangement. The change in structure appears to be due to a direct reaction between two groups within a single molecule. Other support for this idea will be found in connection with the rearrangement of solid acetylchloroaminobenzene (*see* page 79).

Methylene derivatives of aromatic amines are prepared by the action of an alkaline solution of formaldehyde upon aniline and its homologues.

$$CH_2O + 2C_6H_5NH_2 \longrightarrow CH_2(NHC_6H_5)_2 + H_2O$$

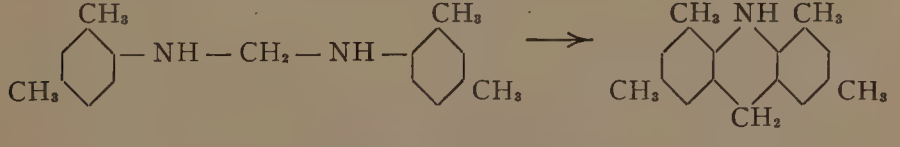
When these compounds are warmed with hydrochloric acid or with an excess of the amine hydrochloride they undergo a rearrangement which results in the attachment of the methylene group to the *para*-carbon atoms of the benzene nuclei. If the *para* position is occupied the migrating group goes to the *ortho* position.

The method employed in preparing the diimine and converting it into the diaminodiphenylmethane is illustrated in an experiment with *para*-toluidine.[14]

A mixture of 214 parts by weight of *para*-toluidine, 50 parts of alcohol and 30-50 parts of potassium hydroxide was warmed on a water bath until a clear solution was obtained. Then, slowly, and with constant shaking, 77 parts of a 39% aqueous solution of formaldehyde was added and the warming was continued for an hour or two. On cooling a good yield of crystals of methylenedi*para*tolylimide was obtained. When this product was warmed with hydrochloric acid for ten or twelve hours diaminoditolylmethane was obtained in the form of colorless needles melting at 92° C.

This reaction resembles the benzidine change. It probably takes place in two stages, the first step resulting in the formation of a semidine. The intermediate product has not been isolated, but semidines, as a rule, are not obtained unless further change is inhibited by substituents in the ring.

Acridine derivatives have been prepared by similar reactions.[15] Thus, methylene chloride and *meta*-4-xylidine when heated in a sealed tube for three hours at 160° C. yields dixylylmethylenediamine. It is a yellow crystalline compound melting at 127° C.-128° C.[16] When these crystals are heated to 270° C.-290° C. they are completely decomposed and from the decomposition products a small yield of tetramethyldihydroacridine can be obtained.

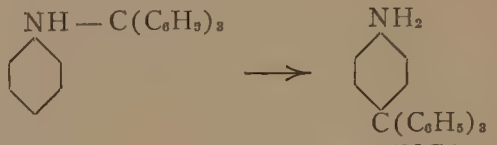


TRIPHENYLMETHYLANILINE

N-triphenylmethylaniline, $C_6H_5—NH—C(C_6H_5)_3$ is prepared by warming triphenylchloromethane dissolved in benzene with a solution of aniline in alcohol. The reaction is completed within fifteen minutes at the temperature of a water bath.[17] The crystalline product melts at 146° C. When heated with half its weight of

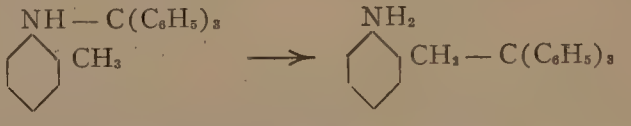
[14] Eberhardt and Welter, *Ber.*, **27**, 1804 (1894).
[15] Senier and Compton, *J. Chem. Soc.*, **91**, 1927 (1907).
[16] Senier and Goodwin, *J. Chem. Soc.*, **81**, 280 (1902).
[17] Elbs, *Ber.*, **17**, 701 (1884); Hemilian, *Ber.*, **17**, 741 (1884); Gomberg, *Ber.*, **35**, 1822 (1902).

zinc chloride for fifteen minutes at 160° C., it is converted into *para*-aminotetraphenylmethane. The latter is obtained from the fused mass by extraction with alcohol after the zinc chloride has been removed by washing with water.[18]



(m.p. 160°C.) (m.p. 249°C.)

According to Van Alphen the N-triphenylmethyl derivative of *o*-toluidine, under similar treatment yields *α*-2-aminophenyl-*βββ*-triphenylethane.



That the triphenylmethyl radical was actually introduced into the methyl group of the *o*-toluidine was proved by diazotizing the substance, boiling with water, and identifying the resulting hydroxy compound by an independent synthesis.

ARYLHYDROXYLAMINES

When heated with sulfuric acid *β*-phenylhydroxylamine is converted into *para*-aminophenol.[19]

Other arylhydroxylamines behave in the same way if there is an unsubstituted *para* or *ortho* position in the ring.

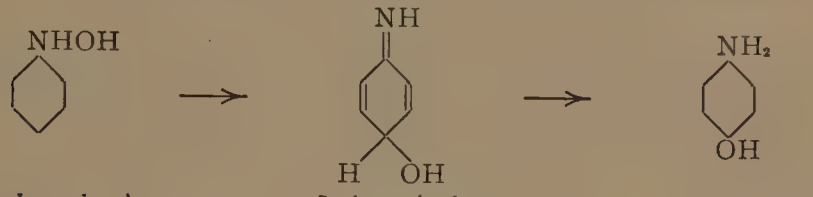
A similar transposition of the hydroxyl group occurs in *para*-alkyl substituted arylhydroxylamines but the main product formed is a substituted hydroquinone. Bamberger believes that in all cases the rearrangement of an arylhydroxylamine goes through an iminoquinol stage. The iminoquinol could not be isolated in the course of the rearrangement of an unsubstituted arylhydroxyl-

[18] Van Alphen, *Rec. trav. chim.*, **46**, 501 (1927).

[19] Gattermann, *Ber.*, **26**, 1844 (1893); Bamberger, *Ber.*, **27**, 1347 (1894); Stieglitz, *Am. Chem. J.*, **46**, 327 (1911); Bamberger and Lagutt, *Ber.*, **31**, 1501 (1898).

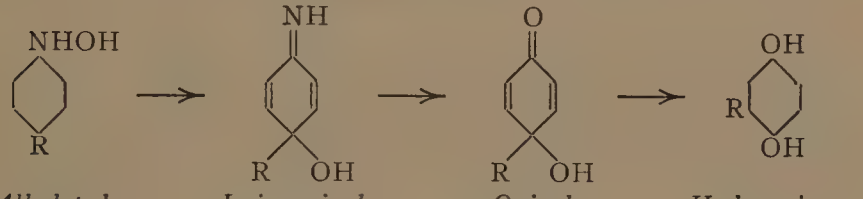
amine, but when certain *para*-alkylated compounds were used derivatives of the iminoquinol were obtained.

In dilute aqueous sulfuric acid there are two main reactions of an iminoquinol. It may be converted into an aminophenol or it may be hydrolyzed to a quinol.[20] The first course predominates with iminoquinoles derived from unsubstituted arylhydroxylamines.



Arylhydroxylamine *Iminoquinol* *Aminophenol*

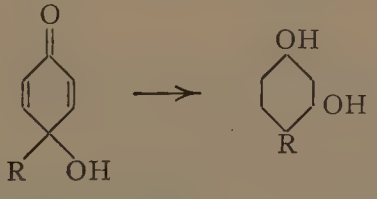
The second course involves the migration of an alkyl radical.



p-Alkylated arylhydroxylamine *Iminoquinol* *Quinol* *Hydroquinone*

Apparently the radical, R, has the same chance to shift in the iminoquinol that it has in the quinol. But the former presents two possibilities, viz., rearrangement and hydrolysis, and hydrolysis is the faster reaction.[21] When, by hydrolysis, the quinol state is reached rearrangement is the only path for further change. In a few instances the quinols have been isolated. They are all converted into the hydroquinones by the application of heat.

It is not always the alkyl radical that migrates. The hydroxyl group may be the one to move. Thus, when a quinol is heated with an alcoholic solution of sulfuric acid a product is formed in which the two hydroxyl groups are in *meta* positions.



[20] For other possibilities see Bamberger, *Ber.*, **33**, 3600 (1900).
[21] Bamberger, *Ber.*, **35**, 3886 (1902).

We are indebted to Zincke, Bamberger and Auwers for exhaustive studies of the quinols and the iminoquinols.[22]

The above reactions are not quantitative. A great variety of by-products have been isolated. Among these may be mentioned diarylamines and azoxy-compounds. There is a tendency toward intermolecular oxidation and reduction in all arylhydroxylamines.

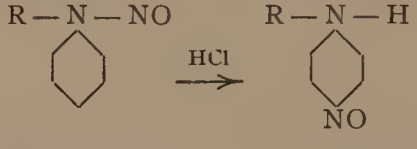
$$2C_6H_5NHOH \longrightarrow C_6H_5NH_2 + C_6H_5NO + H_2O$$

The nitrose compound seldom appears among the products on account of the speed of its reaction with unchanged arylhydroxylamine.

$$C_6H_5-NO + C_6H_5-NHOH \longrightarrow C_6H_5-N(O)-N-C_6H_5 + H_2O$$

NITROSOAMINES

The nitroso group migrates from amino nitrogen to the *para*-position in the ring when an aromatic nitrosoamine is treated with an alcoholic or an aqueous solution of hydrogen chloride. The reaction is known as the Fischer and Hepp rearrangement.[23]



The yield of the *para*-nitroso-derivative is often small. Greater quantities of chlorination products are generally formed. The nitrosoamine or nitrous acid derived from it reacts with chloride ion forming nitrosyl chloride or free chlorine. Since chlorine acts rapidly upon amines, the chlorination reaction generally predominates. Similarly bromination occurs when hydrobromic acid is used. A typical procedure, follows:

A solution of 8 grams of methylphenylnitrosoamine in 40 grams of dry ether at —5°C. was mixed with 24 grams of alcoholic hydrogen bromide. (This was prepared by saturating absolute alcohol with HBr gas at 0°C., then diluting with two volumes of absolute alcohol.) The mixture was

[22] Zincke, *Ber.*, **28,** 3121 (1895); *Ber.*, **34,** 253 (1901); *Ann.*, **320,** 145 (1901); Zincke, Siebert and Reinbach, *Ann.*, **322,** 174 (1902); Zincke and Fries, *Ann.*, **325,** 19 (1902); Zincke and Krügener, *Ann.*, **330,** 61 (1904); Bamberger and Blangey, *Ber.*, **36,** 1625 (1903); Auwers, *Ber.*, **35,** 443, 455 (1902); *Ber.*, **36,** 1861, 3902 (1903); Auwers and Winternitz, *Ber.*, **35,** 465 (1902); Auwers and Keil, *Ber.*, **35,** 4207 (1902).

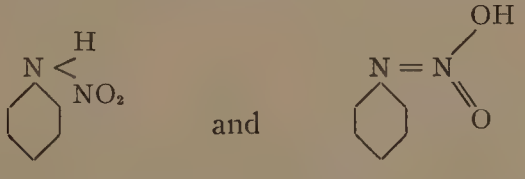
[23] Fischer and Hepp, *Ber.*, **19,** 2991 (1886); **20,** 1247 (1887); Fischer, *Ber.*, **45,** 1098 (1912).

allowed to stand three hours. During this time there was a slow evolution of gas (NO and Br_2) and the formation of a crystalline mass which was found to be a mixture of the hydrobromides of methylaniline, *para*-nitroso-methylaniline and *para*-bromo-aniline.

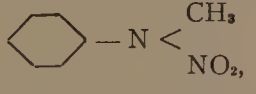
For details concerning the separation and identification of the products see Fischer, *Ber.* **45,** 1100 (1912).

NITROAMINES

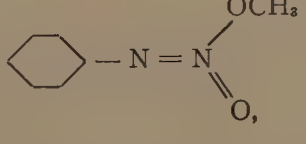
Phenylnitroamine is a colorless crystalline compound (m.p. 46° C.) obtained by nitrating aniline with nitrogen pentoxide [24] or by warming aniline nitrate with acetic anhydride.[25] It is a tautomeric compound corresponding to the formulas



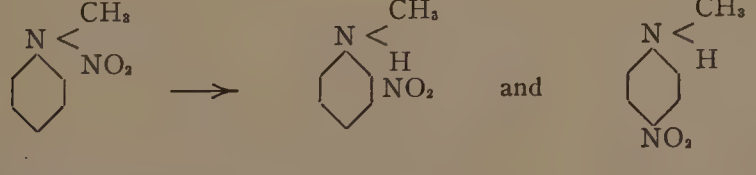
Its sodium salt reacts with methyl iodide, yielding the crystalline α-methyl ester



whereas the silver salt by the same treatment is converted into the β-ester, a yellow oil.[26]

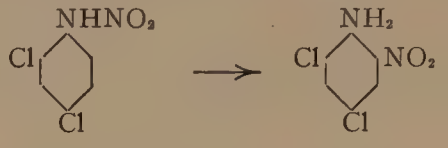


When warmed with sulfuric acid or dissolved in acetic acid which is saturated with hydrogen chloride, phenylnitroamine and its α-esters undergo rearrangements with the production of nitro-anilines.



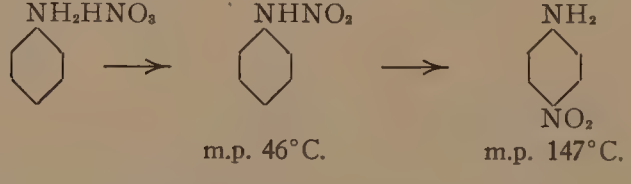
[24] Bamberger, *Ber.*, **27,** 584 (1894).
[25] *Ibid.*, **28,** 399 (1895).
[26] *Ibid.*, **27,** 359 (1894).

Rate measurements have been made on the conversion of 2,4-dichloro-1-nitroaminobenzene to 2,4-dichloro-6-nitroaniline. The reaction follows the unimolecular law.[27]



It has been reported that the nitro group in a nitroamine will replace another radical in the *ortho* or *para* position, giving rise to a product not ordinarily formed by direct nitration.[28] Thus, 2,6-dibromo-1-nitroaminobenzene gives rise to a mixture of 2,6-dibromo-4-nitroaniline and 2,4-dibromo-6-nitroaniline. In the direct nitration of 2,6-dibromoacetanilide no such shift of bromine occurs. The *para*-nitro-derivative only is obtained.

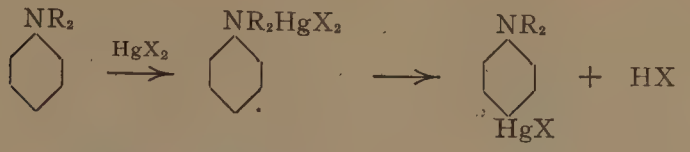
This rearrangement probably occurs regularly in the nitration of any aromatic amine. Aniline, for example, forms a nitrate which loses water in the presence of a dehydrating agent, such as sulfuric acid or acetic anhydride, leaving a nitroamine. This being unstable in acid solution changes to the isomeric *ortho* or *para* nitro-body.



With acetic acid, aniline yields an acetate which readily loses a molecule of water, forming acetanilide. But the acetyl group in the monoacetyl derivative does not migrate. The nitro-group is more mobile and special care has to be exercised if the N-nitro-compound is to be isolated.

The theory has been advanced that all nuclear substitutions in aromatic amines are preceded by the formation of addition products.[29] In the mercurization of aromatic amines Kharasch and Jacobson [30] found the first step to be addition of mercuric chloride or mercuric acetate, HgX_2, to the amino group. This is followed by a shift to the *ortho* or *para* position.

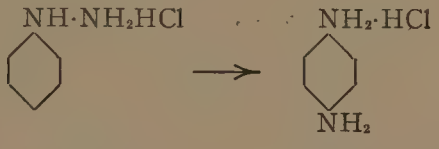
[27] Kipping, Reed, et al., *Chem. News*, **98**, 164 (1908).
[28] Orton and Smith, *J. Chem. Soc.*, **87**, 389 (1905).
[29] Armstrong, *J. Chem. Soc.*, **51**, 258, 583 (1887); Bamberger, *Ber.*, **27**, 584 (1894).
[30] Kharasch and Jacobsohn, *J. Am. Chem. Soc.*, **43**, 1894 (1921).



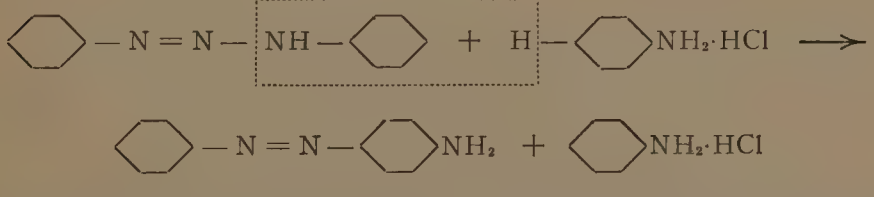
In support of this mechanism they cite the fact that *para*-nitrodimethylaniline, which is too weak a base to form an aminomercury salt, cannot be mercurized in the ring.

HYDRAZINES, HYDRAZOBENZENES AND DIAZOAMINO COMPOUNDS

Phenylhydrazine hydrochloride, when heated to 200° C., is partly converted into *para*-phenylenediamine.



The conversion of diazoaminobenzene into aminoazobenzene is another example of the Hofmann rearrangement. Diazoaminobenzene is formed by coupling aniline with benzenediazonium chloride. The yellow crystalline product decomposes, when heated with aqueous hydrochloric acid, yielding phenol, aniline and nitrogen. If, however, the compound is warmed with aniline hydrochloride, it is converted into aminoazobenzene, the hydrochloride of which appears in the form of blue crystals. An eighty percent yield is easily obtained. When ammonia is added to an alcoholic solution of the hydrochloride, the free base crystallizes out as orange-yellow leaflets. Gattermann assumes a double decomposition between the diazoamino compound and aniline hydrochloride as indicated by the equation

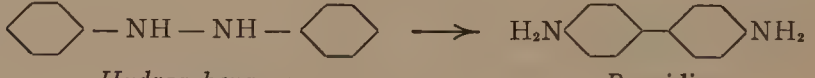


The aniline formed in the reaction is a stronger base than aminoazobenzene and in this way Gattermann accounts for the capacity of a limited quantity of the hydrochloride to change a relatively large quantity of the diazoamino compound.

Yokojima has reported a series of attempts to obtain aminoazobenzene by heating diazoaminobenzene or its hydrochloride alone and in alcoholic solution. These efforts failed unless free aniline also was present. He regards the change as a metathesis between diazoaminobenzene hydrochloride and free aniline [*J. Soc. Chem. Ind.* (Japan) **31**, 100 (1928)].

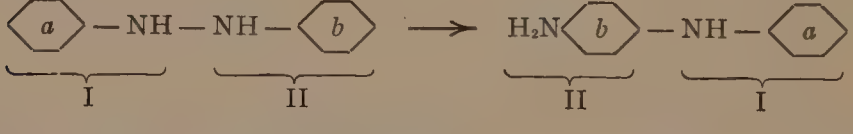
The reaction, however, is similar in every respect to other examples of the Hofmann rearrangement and it seems unnecessary to devise a special mechanism for it. If alkylaryl amines, nitroamines and hydrazo compounds are converted into primary amines through direct reactions between two groups within a single molecule, it is probable that the same course is followed by diazoamino compounds. Direct reaction between the two groups is not a definitely established mechanism, but the similarities in structures of compounds that are susceptible to the Hofmann change and the similarities in the results achieved by an almost uniform procedure establish a strong presumption that the mechanisms are identical.

The benzidine change is induced by treating hydrazobenzene with a concentrated aqueous solution of hydrogen chloride. The reaction is completed within fifteen minutes at room temperature.

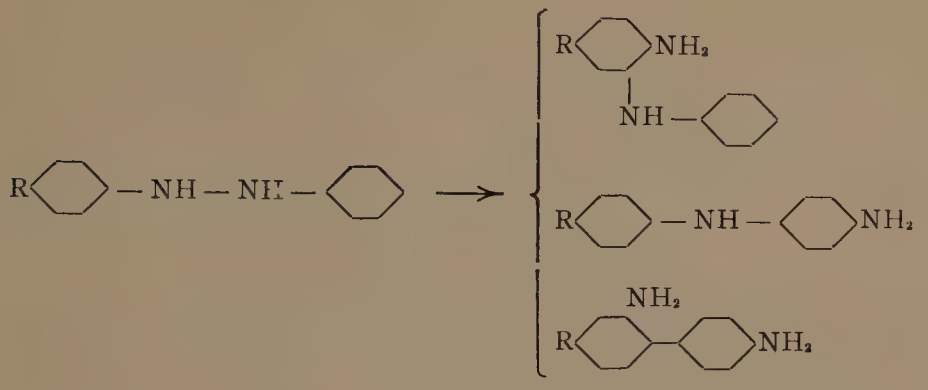


Hydrazobenzene *Benzidine*

In this rearrangement, the ordinary Hofmann reaction occurs twice. In the first place group I shifts to the *para* position in nucleus *b*.

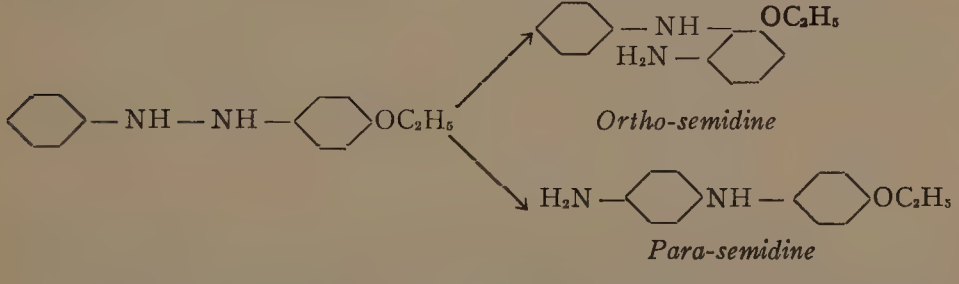


In the second place, group II shifts to the *para* position in nucleus *a*. In each case, the migrating group attaches in its new position by the same valence bond that is released when the shift occurs. If the *para* position in one ring is occupied by a radical other than hydrogen, benzidine can not be formed but three other possibilities exist. An *ortho*-semidine, a *para*-semidine or a diphenyldiamine may be produced.



Very little of the diamine appears in the reaction mixture but the two semidines are always present, the *para* compound usually predominating. Hydrazo compounds having a *para* substituent in each of the rings yield *ortho*-semidines only.[31]

The character of the semidine rearrangement was established by Jacobson and his colleagues in an exhaustive study of the reduction products of azophenol ethers.[32] It was shown that stannous chloride and hydrochloric acid react with a compound of the type $C_6H_5—N{=}N—C_6H_4OR$ to yield a *para*-semidine, an *ortho*-semidine, aniline and the aminophenol ether, $ROC_6H_4NH_2$. The first two products are formed by rearrangement of the primary reduction product and the last two by further reduction and cleavage.

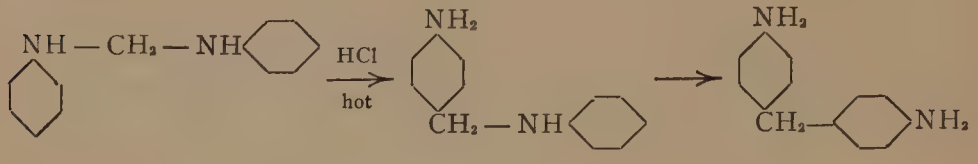


In *dipara*-substituted azo compounds the shift is, necessarily, to the *ortho* position exclusively, but in many cases Jacobson obtained larger yields of *ortho* than of *para* compounds when both positions were free to receive the migrating group. In all cases of *ortho*-semidine formation from azophenol ethers he found that the hydrogen displaced by the migrating radical was in the nucleus to which the *para* alkoxyl group was attached.

[31] For a complete review of the chemistry of hydrazo compounds, see Jacobson, *Ann.*, **427**, 142 (1922).

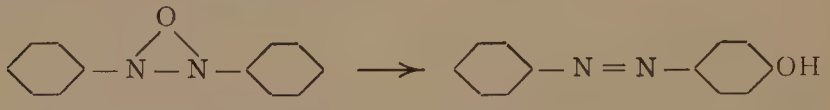
[32] Jacobson, *Ann.*, **287**, 97 (1895); *Ber.*, **26**, 700 (1893).

The salts of methylene dianilines, when heated, rearrange in the same way.[33]



AZOXYBENZENE AND AMINE OXIDES

When azoxybenzene is warmed with sulfuric acid it is converted into *para*-hydroxyazobenzene.[34]



The best yield is obtained by using approximately ten times as much acid as azoxybenzene and by keeping the temperature between 75° C. and 80° C. Acid having the composition represented by the formula $H_2SO_4 \cdot H_2O$ is a suitable reagent. Wide variations, however, in concentration of acid, in quantity of acid and in temperature are permissible. The principal by-products of this reaction are azobenzene and hydroxyazobenzenesulfonic acid.

The reactions of amine oxides are related to this rearrangement. When a cold aqueous solution of the amine oxide is saturated with sulfur dioxide and permitted to stand for several hours the following reaction occurs.[35]

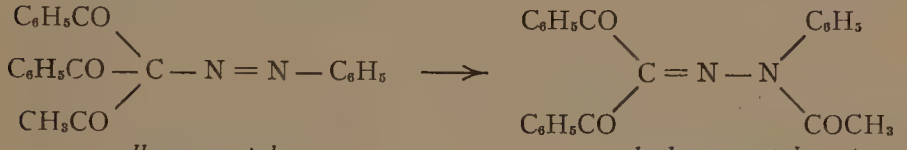
The rearrangement of a brominated benzenediazonium chloride to a chlorinated benzenediazonium bromide occurs when the former is warmed in a mixture of alcohol and ether.[36]

[33] Eberhardt and Welter, *Ber.*, **27**, 1804 (1894); Meyer and Rohmer, *Ber.*, **33**, 250 (1900); Von Braun and Kruber, *Ber.*, **45**, 2977 (1912).
[34] Wallach and Belli, *Ber.*, **13**, 525 (1880); Wallach and Kiepenheuer, *Ber.*, **14**, 2617 (1881); Lachman, *J. Am. Chem. Soc.*, **24**, 1178 (1902).
[35] Bamberger and Tschirner, *Ber.*, **32**, 1882 (1899).
[36] Hantzsch and Smythe, *Ber.*, **33**, 505 (1900).

The reaction never results in substitution of chlorine for bromine in a *meta* position. It takes place slowly but at a measurable rate in aqueous solution and more rapidly in anhydrous solvents. It has a high temperature coefficient and proceeds in strict agreement with the unimolecular law.

The same change occurs when *para*-chlorobenzenediazonium thiocyanate is warmed with a dilute alcoholic solution of hydrogen chloride. The thiocyanate ion replaces the chlorine and *para* thiocyanobenzenediazonium chloride is formed.[37] These are unexpected results, for ordinarily a halogen atom is not easily removed from the benzene ring.

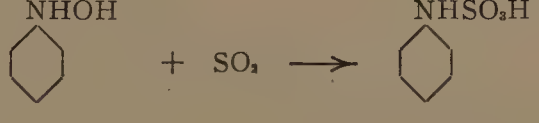
Benzene-azo-acetyldibenzoylmethane changes at its melting point into an isomeric hydrazone.[38]



yellow crystals m.p. 90° C. — *colorless crystals* m.p. 188° C.

SULFAMIC ACIDS AND AMIDES OF SULFONIC ACIDS

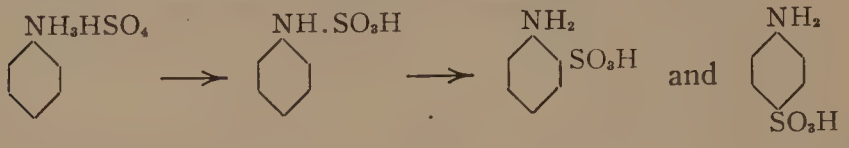
Phenylsulfamic acid, $C_6H_5NHSO_3H$, isolated only in the form of salts, is made by treating a solution of aniline in chloroform with sulfur trioxide[39] or by the action of sulfur dioxide upon phenylhydroxylamine.[40]



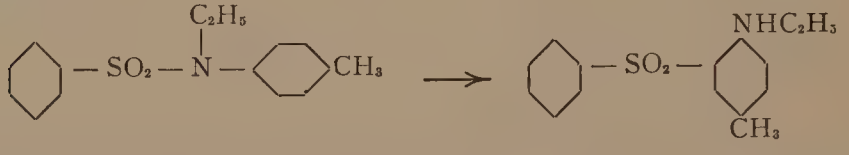
In four or five hours at 180° C. a salt of this acid is converted into a salt of sulfanilic acid. The same change is involved in the preparation of sulfanilic acid from aniline sulfate by the action of heat. Water is lost from the aniline salt and a sulfamic acid is formed as an intermediate product. This rearranges to *ortho* or to *para* aminobenzenesulfonic acid. The temperature of the reaction

[37] Hantzsch and Hirsch, *Ber.*, **29**, 947 (1896); Hantzsch, *Ber.*, **29**, 1067 (1896).
[38] Dimroth and Hartmann, *Ber.*, **40**, 4460 (1907).
[39] Traube, *Ber.*, **24**, 360 (1891).
[40] Bamberger and Hindermann, *Ber.*, **30**, 654 (1897).

determines the quantity of each of these products. At temperatures above 180° C. the *para* compound is obtained exclusively.[41]



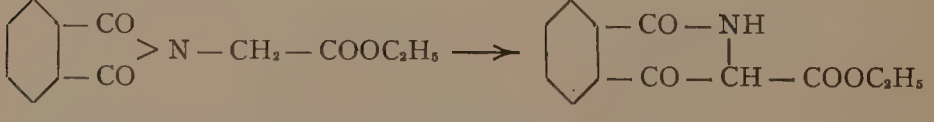
Sulfoamides derived from arylsulfonyl chlorides and alkylaryl amines undergo similar changes in structure when warmed on a water bath with 80% sulfuric acid. The shift is generally to a position *ortho* to the nitrogen. The resulting compounds are sulfones.[42]



Corresponding compounds derived from primary amines have hydrogen in place of the alkyl radical attached to nitrogen. These sulfoamides are hydrolyzed by treatment with acid but no by-products of the sulfone type appear.

The study of this reaction was extended by Witt and his associates to the sulfoamide derived from *m*-nitrobenzenesulfonyl chloride and *p*-toluidine, and to its N-methyl derivative. The former dissolves in dilute aqueous alkalies with the development of an orange color. It is hydrolyzed but not otherwise changed by warming with acids. The N-methyl derivative is insoluble in alkalies and is converted by concentrated sulfuric acid into the corresponding sulfone, the sulfur linkage shifting to a position *ortho* to the nitrogen as indicated above.

A different type of shift from nitrogen to carbon occurs in the transformation of ethyl phthalimidoacetate into a derivative of oxycarbostyril. The reaction is induced by an alcoholic solution of sodium ethylate.[43]



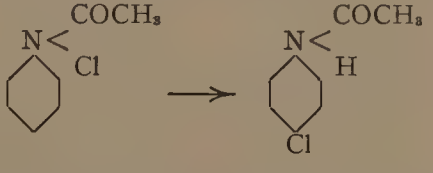
[41] Bamberger and Kunz, *Ber.*, **30**, 2274 (1897).
[42] Witt and Truttwin, *Ber.*, **47**, 2786 (1914).
[43] Gabriel and Colman, *Ber.*, **33**, 980 (1900); **35**, 1358 (1902).

At temperatures above 210° C. ethyl *iso*cyanide is converted into propionitrile.[44]

$$C_2H_5NC \longrightarrow C_2H_5CN$$

ACYLHALOGENAMINOBENZENES

When a cold saturated aqueous solution of acetanilide is treated with hypochlorous acid acetylchloroaminobenzene is formed.[45] The product can be kept for an indefinite period if dry and protected from light. In pure water it is stable in the dark at a low temperature, if the solution is exposed to light, there is a slow conversion of the compound into *ortho*- and *para*-chloroacetanilide.[46] The presence of hydrochloric acid causes rapid and almost quantitative conversion of the compound into the chloroacetanilides.[47] The reaction follows the unimolecular law.[48] The simplest representation of this irreversible change is indicated as follows:



The actual mechanism of the reaction may not be as simple as this formulation appears.

Acree and Johnson agree with Orton [49] that the halogen acid employed as a catalyst forms an addition product with acetylchloroaminobenzene and this, in turn, undergoes rearrangement.

$$C_6H_5NClAc + HCl \longrightarrow C_6H_5NHCl_2Ac \longrightarrow$$
$$C_6H_5NHCl_2Ac \longrightarrow ClC_6H_4NHAc + HCl$$

They report that acetylchloroaminobenzene and hydrobromic acid yield *para*-bromoacetanilide, and the same product (bromoacet-

[44] Nef, *Ann.*, **280**, 291 (1894).

[45] For details relating to methods of preparation see Slosson, *Ber.*, **28**, 3265 (1895); Chattaway and Orton, *J. Chem. Soc.*, **1901**, 277.

[46] The yield is 60% to 80% *para*-chloroacetanilide and 20% to 40% *ortho*-chloroacetanilide. When acetanilide is treated with free chlorine the distribution ratio between the two monochloroderivatives produced is about the same.

[47] Bender, *Ber.*, **19**, 2272 (1886); Comstock and Kleeberg, *Am. Chem. J.*, **12**, 500 (1890); Blanksma, *Rec. trav. chim.*, **22**, 290 (1903).

[48] Blanksma, *Rec. trav. chim.*, **21**, 366 (1902); Rivett, *Z. physik. Chem.*, **82**, 201 (1913); Mathews and Williamson, *J. Am. Chem. Soc.*, **45**, 2574 (1923).

[49] Acree and Johnson, *Am. Chem. J.*, 37, 410 (1907). Orton, *Proc. Roy. Soc.*, **71**, 156 (1902).

anilide) is formed when acetylbromoaminobenzene is treated with hydrochloric acid. This is a logical consequence if the addition product is formed for it would be $C_6H_5NHClBrAc$ in either case.

In a report to the British Association for the Advancement of Science, Kipping [50] and his co-workers say that the primary action is hydrolysis of the chloroamine with the production of hypochlorous acid and acetanilide. The hypochlorous acid reacts with hydrochloric acid, to yield free chlorine, and finally, as an independent side reaction, the acetanilide is chlorinated in the *para*-position or in the *ortho*-position.

$$C_6H_5NClAc + H_2O \rightleftharpoons C_6H_5NHAc + HClO \quad [1]$$

$$HClO + HCl \rightleftharpoons H_2O + Cl_2 \quad [2]$$

$$C_6H_5NHAc + Cl_2 \longrightarrow ClC_6H_4NHAc + HCl \quad [3]$$

In support of this mechanism it is pointed out that:

(1) Hypochlorous acid is the normal hydrolysis product of the chloroamine.

(2) The equilibrium represented in equation [2] is of such a character that in 0.1 *N* HCl or any more concentrated solution the hypochlorous acid is almost completely converted into free chlorine.

(3) Chlorine acts rapidly upon acetanilide to form *para*-chloroacetanilide.

To account for the fact that in the light the rearrangement occurs at a measurable rate in solutions to which no hydrochloric acid has been added, it is assumed that by hydrolysis acetanilide and hypochlorous acid are formed, and by a continuation of the hydrolysis process some of the acetanilide is converted into aniline and acetic acid. Aniline reduces hypochlorous acid to hydrochloric acid and from this point the reaction can proceed as outlined above. The idea is supported by the fact that hydrochloric acid appears as a reaction product. When the rearrangement is induced by hydrogen chloride the amount of this acid present at the end of the reaction is slightly greater than the amount originally introduced. The appearance of color during the process lends further support to this view. The color is said to be due to an oxidation product of aniline—the same colored compound that is formed by

[50] See the report of a committee consisting of F. S. Kipping, K. J. Orton, S. Ruhemann and J. T. Hewitt, assisted by W. H. Gray, *Chem. News*, **108**, 155 (1913). For hydrolysis constants of chloroamines see F. G. Soper, *J. Chem. Soc.*, **127**, 98 (1925).

direct treatment of aniline with bleaching powder. Acetanilide does not reduce hypochlorous acid, hence the necessity of assuming hydrolysis of a limited portion of the acetanilide to aniline and acetic acid. One mol of free aniline reduces several mols of hypochlorous acid.[51]

According to this view the specific effect of hydrochloric acid as a catalyst is due to its influence in suppressing the hydrolysis of chlorine.

$$Cl_2 + H_2O \rightleftharpoons HClO + H^+ + Cl^-,$$

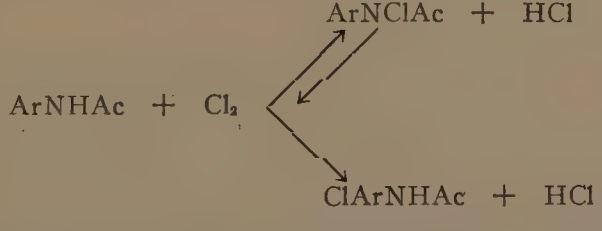
$$\frac{(HClO)(H^+)(Cl^-)}{(Cl_2)} = K.$$

The fact that the catalytic effect of hydrochloric acid in this reaction is roughly proportional to the square of its concentration has been confirmed by many investigators.[52]

It must be remembered, however, that the rearrangement occurs more readily in non-aqueous media than in the presence of water. Glacial acetic acid, absolute alcohol and benzene are solvents that promote the reaction. The actual mechanism therefore does not always involve hydrolysis.

Orton and Jones assume that the rearrangement, as induced by hydrochloric acid, is accomplished by a comparatively slow reversible metathesis between the hydrogen chloride and acetylchloroaminobenzene followed by a very rapid substitution of chlorine for hydrogen in the ring.[53]

A slightly different formulation assumes that two rapid reactions occur between chlorine and acetanilide. One of these is reversible and the other irreversible. There is finally complete conversion to the *para*-chloroacetanilide on account of the irreversibility of the process by which it is produced.[54]



[51] Kipping, Orton and others, *Chem. News*, **108**, 155 (1913).
[52] Blanksma, *Rec. trav. chim.*, **22**, 290 (1903); Rivett, *Z. physik. Chem.*, **82**, 201 (1913); Harned and Seltz, *J. Am. Chem. Soc.*, **44**, 1475 (1922).
[53] Orton and Jones, *Brit. Assoc. Advancement Sci. Repts.*, **1910**, p. 85.
[54] Orton and King, *J. Chem. Soc.*, **99**, 1369 (1911).

The fact that water retards the rearrangement is explained by the effect of water on the equilibrium

$$ArNHAc + Cl_2 \rightleftharpoons ArNClAc + HCl$$

In glacial acetic acid the products on the right-hand side can not be detected but as the solvent is diluted the equilibrium shifts so as to permit more and more of the chloroamine to appear. In 50% acetic acid only a trace of free chlorine is present.

Rivett measured the rate of rearrangement of acetylchloroaminobenzene in acetic acid with various concentrations of hydrochloric acid at different temperatures. The initial concentration of the chloroamine was usually 0.2 *M*. The reaction was followed by titrating samples with 0.02 *N* thiosulfate.

$$C_6H_5NClAc + 2HI \longrightarrow C_6H_5NHAc + HCl + I_2$$
$$2Na_2S_2O_3 + I_2 \longrightarrow Na_2S_4O_6 + 2NaI$$

Light effects were eliminated by painting the containers black. The values of K were calculated from the formula

$$k = \frac{l}{t} \log_{10} \frac{A_o}{A_t}.$$

A_o is the volume of thiosulfate required to titrate the unchanged sample and A_t is the volume of thiosulfate required after t minutes.

In connection with his measurements Rivett tried to obtain a relationship between the velocity constants and the concentrations of hydrochloric acid used. The closest approach to a generalization agreeing with his actual determinations is represented by an equation including at least two arbitrary constants. There is, however, a strict proportionality between the velocity of the reaction and the product of the *activities* of the chloroamine, the hydrogen ion and the chloride ion.[55]

All of the mechanisms thus far reviewed show how hydrochloric acid is involved in the reaction. But acetylchloroaminobenzene in dry benzene solution without a halogen acid or any other electrolyte is changed to *para*-chloroacetanilide on exposure to light. Nor

[55] Harned and Seltz, *J. Am. Chem. Soc.*, **44**, 1475 (1922).
An exhaustive study of this reaction has been made by C. Ch. J. Fontein. Rate measurements were made on the rearrangement of acetylchloroaminobenzene and of other acylhalogen amines in various solvents and at several temperatures. The results have been published by Mulder and Zoon, Leiden, in the form of a monograph entitled "Intramoleculaire Omzettingssnelheden bij Arylacylhalogeenaminen."

is the solvent necessary. Dry crystals of the chloroamine when exposed to light gradually go over to *ortho*- and *para*-chloroacetanilide, and the same change can be brought about in a few minutes by heat alone. Benzoylchloroaminobenzene undergoes the rearrangement in the same way.[56]

The photochemical conversion of acetylchloroaminobenzene has been studied in detail.[57] The most effective wave lengths for this reaction are between 2700 Å and 2400 Å as indicated by curve I, Fig. 1, in which the absorption coefficient e is plotted against wave lengths.[58]

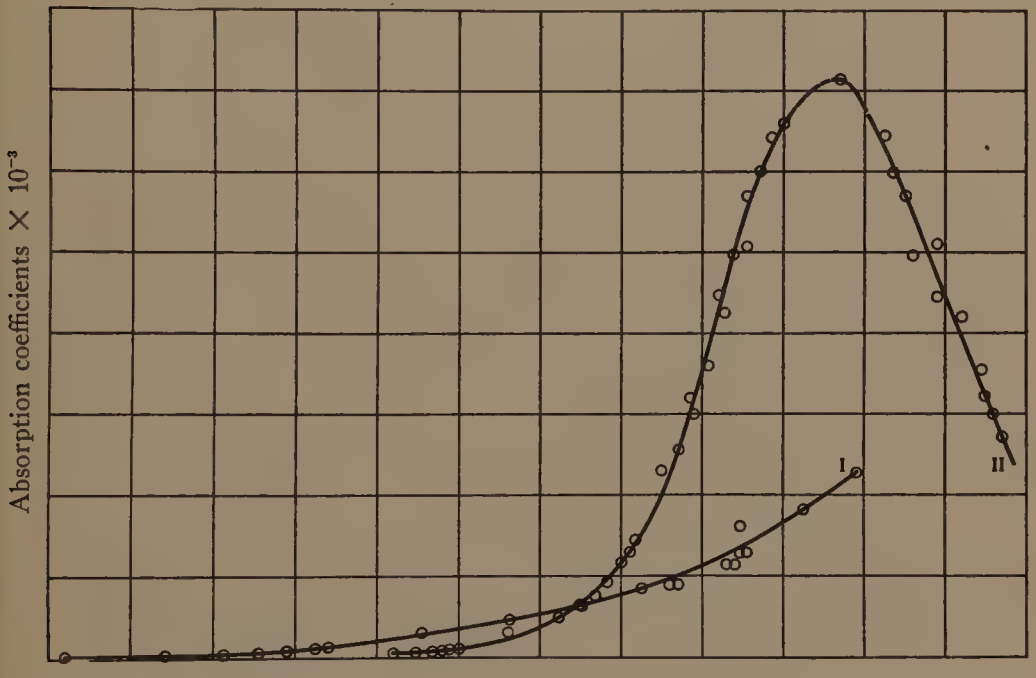


FIG. 1.—Wave lengths in Ångstrom units.

The value of e is obtained from the equation

$$\frac{I_t}{I_o} = 10^{-ecd},$$

in which I_o is the intensity of the light of given wave length that falls upon the solution, I_t is the intensity of the light after passing through the solution, c is the concentration of the solution in mols

[56] Chattaway and Orton, *J. Chem. Soc.*, **75**, 1053 (1899).
[57] Blanksma, *Rec. trav. chim.*, **21**, 366 (1902); **22**, 290 (1903); Mathews and Williamson, *J. Am. Chem. Soc.*, **45**, 2574 (1923).
[58] Porter and Wilbur, *J. Am. Chem. Soc.*, **49**, 2145 (1927).

per liter, d is the thickness of the layer (cm.) that the light traverses, and e is the absorption coefficient. Curve II is a corresponding plot of the ultraviolet absorption coefficients for *para*-chloroacetanilide.

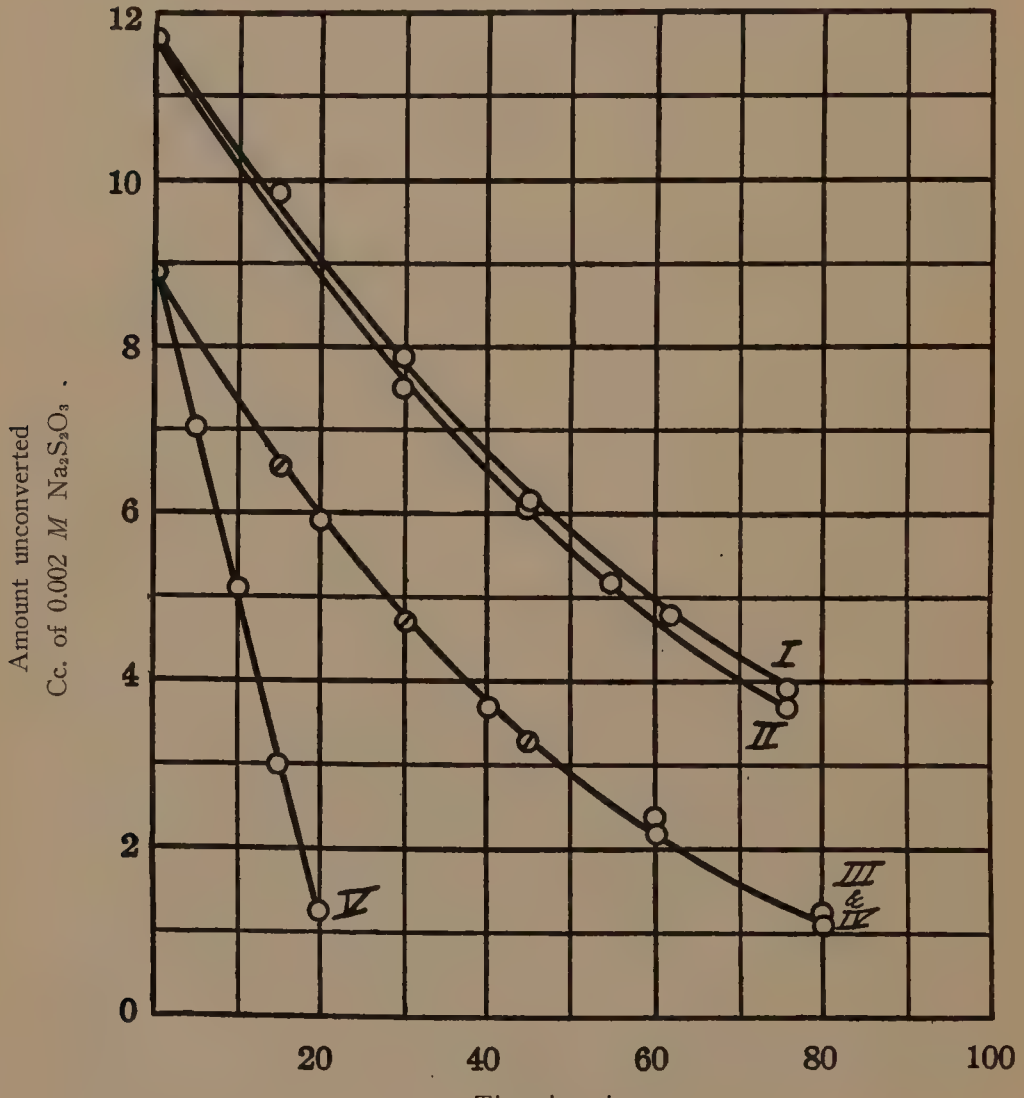


FIG. 2.

The rate of the photochemical change of acetylchloroaminobenzene in various solvents as induced by exposure to a mercury vapor lamp was measured by Mathews and Williamson under carefully controlled conditions. Some of their results are shown in Fig. 2.

Their stock solution was prepared as follows:

1.6950 grams acetylchloroaminobenzene was dissolved in 100 cc. of glacial acetic acid and diluted to 1 liter with distilled water. The solution was kept in a brown bottle in an ice chest. Samples were titrated from time to time with sodium thiosulfate to determine the dark reaction which proved to be negligible.

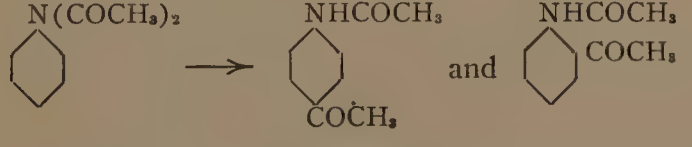
Each curve refers to the rearrangement of a 0.01 *M* solution of acetylchloroaminobenzene in the following solvents:

Curve I 10% acetic acid.
Curve II 10% acetic acid plus 2% sodium acetate.
Curve III Benzene pure.
Curve IV Benzene pure.
Curve V Benzene recovered from runs used in III and IV.

Mathews and Williamson found that in dilute acetic acid (up to 20%) the reaction proceeds only under the influence of light. In glacial acetic acid the reaction is initiated by light but continues in the dark. In absolute alcohol also the reaction continues in the dark after having been started by light. In 95 per cent alcohol the reaction in a 0.01 *M* solution stops when the light is turned off, but in a 0.04 *M* solution the change initiated by light continues at a diminished rate in the dark. In benzene solution also the reaction must be started by light but it continues in the dark at a diminished rate.

DIACYLANILIDES

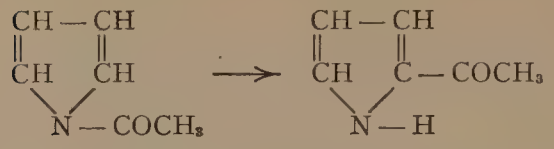
Although acetanilide fails to yield aminoacetophenone the diacetyl derivative of aniline is readily converted by heat into acetylaminoacetophenone.[59] Other diacyl anilides are changed in the same way to the corresponding acylaminoketones.



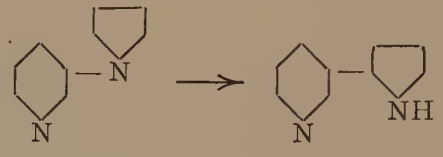
PYRROLE

N-acetylpyrrole is converted into α-acetylpyrrole by heating to 250° C.-280° C. in a sealed tube.[60]

[59] Chattaway, *J. Chem. Soc.*, **85**, 386 (1904).
[60] Ciamician and Magnaghi, *Ber.*, **18**, 1828 (1885); Ciamician and Silber, *Ber.*, **20**, 698 (1887).



Potassium pyrrole reacts with alkyl iodides yielding N-alkyl derivatives which change, when heated, into α-alkylpyrroles.[61] The phenyl and pyridyl groups likewise migrate from nitrogen to the α-carbon atom. It was through the application of this general reaction that N-β-pyridylpyrrole was converted into α-β-pyridylpyrrole in the synthesis of nicotine.[62]



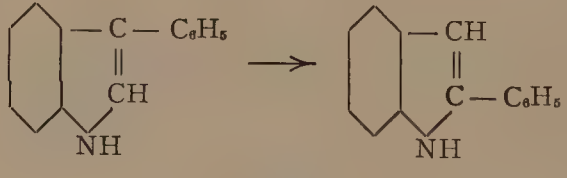
N-β-Pyridylpyrrole *α,β-Pyridylpyrrole*

Pyrrole is made by dry distillation of ammonium mucate.

$$\begin{matrix}CHOH-CHOH-COONH_4\\ |\\ CHOH-CHOH-COONH_4\end{matrix} \longrightarrow \begin{matrix}CH=CH\\ |\\ CH=CH\end{matrix}\!>NH + NH_3 + 2CO_2 + 4H_2O$$

In an exactly analogous manner N-β-pyridylpyrrole is made by heating the mucate of β-aminopyridine.

Pyrrole derivatives having substituents in the α-position are more stable than the corresponding β-compounds. This seems to be the case also with indole derivatives. It is reported that β-phenylindole is changed to α-phenylindole by the action of zinc chloride at 170° C.[63]



PYRIDINE

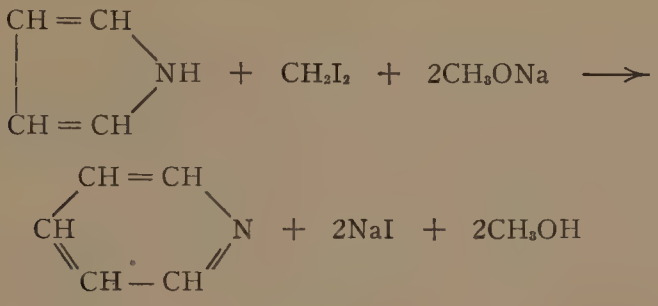
By treatment with methylene iodide and sodium methylate at 200° C., pyrrole is converted into pyridine.[64]

[61] Ciamician and Zanetti, *Ber.*, **22**, 659, 2518 (1889); Zanetti, *Ber.*, **22**, 2515 (1889).

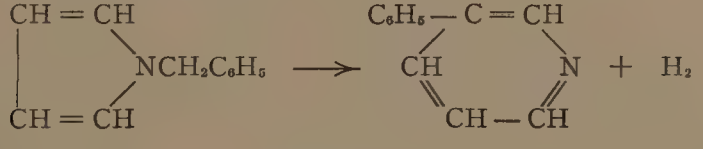
[62] Pictet and Crépieux, *Ber.*, **28**, 1904 (1895); Pictet and Crépieux, *Ber.*, **31**, 2018 (1898); Pictet and Ratschy, *Ber.*, **37**, 1225 (1904).

[63] Fischer and Schmidt, *Ber.*, **21**, 1811 (1888).

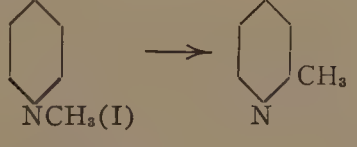
[64] Dennstedt and Zimmermann, *Ber.*, **18**, 3316 (1885).



It is assumed that the methylene group enters the pyrrole nucleus between the α and β carbon atoms for β-substituted pyridines are obtained when aryl derivatives of methylene iodide are employed. When N-methylpyrrole is passed through a glass tube which is heated to dull redness the major portion of the compound is converted into α-methylpyrrole but about ten percent. of it is changed to pyridine. In this case hydrogen escapes as a by-product. The experiment gives no clue as to the point of ingress of the methyl carbon atom into the pyrrole nucleus. When N-benzylpyrrole is subjected to the same treatment the products formed are α-benzylpyrrole and β-phenylpyridine. The appearance of the latter indicates the entrance of the methylene carbon between the α and β atoms of the pyrrole ring.[65]



Pyridinium compounds are susceptible to the Hofmann type of rearrangement. Thus at 300° C. methylpyridinium iodide is converted into α-picoline.[66]

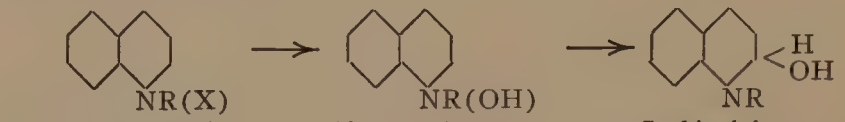


The shift is not confined to the α-position. The corresponding γ-compound also is formed. Ladenberg prepared many α- and γ-pyridines in this way.[67]

[65] Pictet, *Ber.*, **38**, 1946 (1905); Ciamician, *Ber.*, **37**, 4200 (1904).
[66] Lange, *Ber.*, **18**, 3436 (1885).
[67] Ladenburg, *Ber.*, **16**, 1410, 2058 (1883); **18**, 2961 (1885); **20**, 1647 (1887); Ladenburg, *Ann.*, **247**, 1 (1888); **279**, 344 (1894).

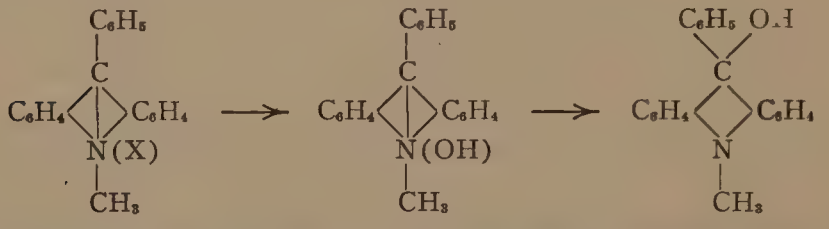
QUINOLINE

Quinoline and *iso*quinoline form addition products with alkyl halides and these salt-like compounds react with silver hydroxide or potassium hydroxide to form nitrogen bases. The latter rearrange to carbinol bases.



Quinolinium halide — *Nitrogen base* — *Carbinol base* (pseudo ammonium base)

Acridinium halides behave in the same way.



The nitrogen base ionizes and the carbinol or pseudo base does not. When one equivalent of potassium hydroxide is added to an aqueous solution of the acridinium salt the conductivity of the solution corresponds to that of pure potassium hydroxide of the same concentration. The conductivity gradually approaches zero as the transformation proceeds.[68]

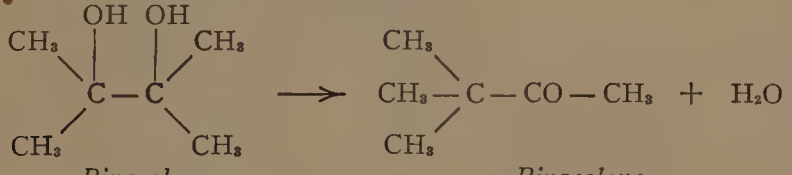
[68] Hantzsch and Kalb, *Ber.*, **32**, 3109 (1899).

Chapter III

Migrations from Carbon to Carbon.

PINACOLS

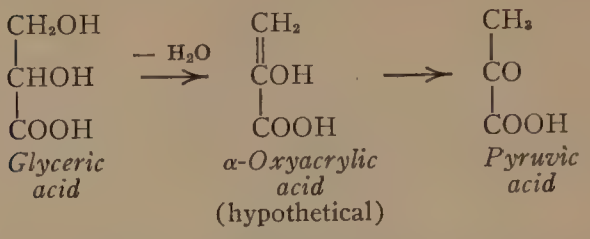
A ditertiary alcohol known as a pinacol is obtained from a ketone by reduction. Tetramethyl glycol, commonly called pinacol, is the principal product obtained when acetone is reduced by mercuric chloride and magnesium in benzene.[1] Other reducing agents may be employed with less satisfactory results.[2] Fittig obtained the compound by reducing acetone with sodium.[3] A sodium derivative of acetone, $CH_3—CONa{=}CH_2$, is probably the first product formed.[4] When pinacol is heated with sulfuric acid it is converted into an unsymmetrical ketone called pinacolone.[5] This reaction is known as the pinacol rearrangement.



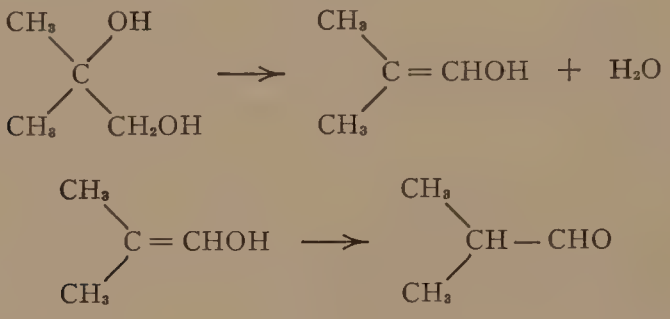
Pinacol *Pinacolone*

In a study of the dehydration products of hydroxy acids Erlenmeyer [6] made the observation that in the aliphatic series when a reaction results in the attachment of a hydroxyl group to a carbon atom which is bound by a double bond to another atom, a rearrangement occurs with the establishment of a carbonyl group.[7] Thus glyceric acid, when heated, yields pyruvic acid presumably through the following course:

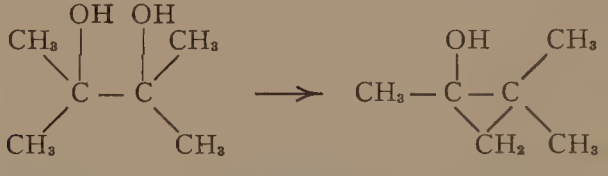
[1] "Organic Syntheses," John Wiley and Sons, **1925**, V, 87.
[2] Kipping and Perkin, *Trans. Chem. Soc.*, **59**, 214 (1891); Acree, *Am. Chem. J.*, **29**, 588 (1903).
[3] Fittig, *Ann.*, **110**, 23 (1859).
[4] Freer, *Am. Chem. J.*, **15**, 582 (1893); Taylor, *Trans. Chem. Soc.*, **89**, 1258 (1906).
[5] Fittig, *Ann.*, **114**, 56 (1860). In the older literature pinacol is called pinacone and pinacolone is called pinacoline.
[6] Erlenmeyer, *Ber.*, **14**, 320 (1881).
[7] Aromatic enols are more stable and in some aliphatic compounds the enol form is stable enough to permit isolation.



Erlenmeyer regarded all rearrangements of glycols as examples of this type. The conversion of *iso*butylene glycol into *iso*butyric aldehyde he used as another illustration.



In the application of this view to the pinacols a trimethylene derivative was assumed to be the dehydration product.



The formation of a cyclopropane as an intermediate has been considered probable by many investigators.[8] Such a mechanism can be applied to rearrangements of monohydric alcohols, where the formation of an ethylene oxide is impossible.[9] It will be referred to later in connection with the Wagner rearrangement.

Lindner [10] accepted Erlenmeyer's view, but Montagne showed that the extension of this theory to the aromatic pinacols would lead to results not in harmony with the facts.[11] Thus the rearrange-

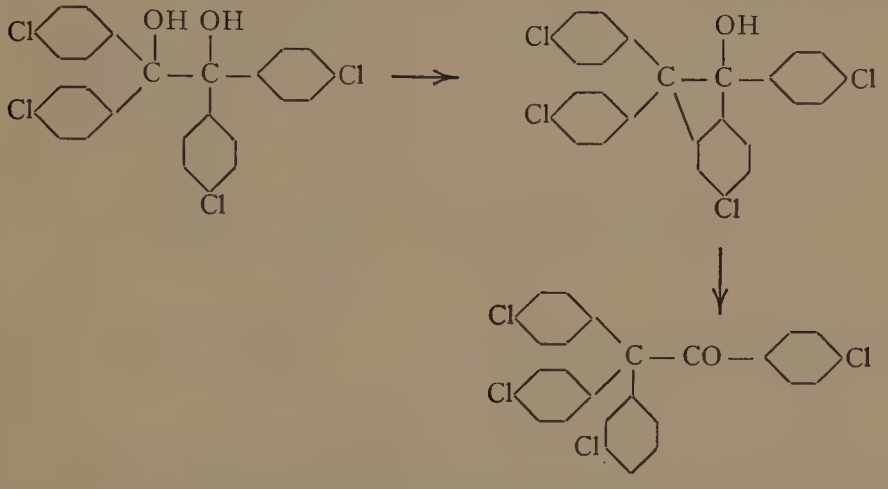
[8] Ruzicka, *Helv. Chim. Acta.*, **1**, 110 (1918); Zumpfe, *Monatsh.*, **25**, 124 (1904).

[9] Ingold, *J. Chem. Soc.*, **123**, 1706 (1923).

[10] Lindner, *Monatsh.*, **32**, 403 (1911).

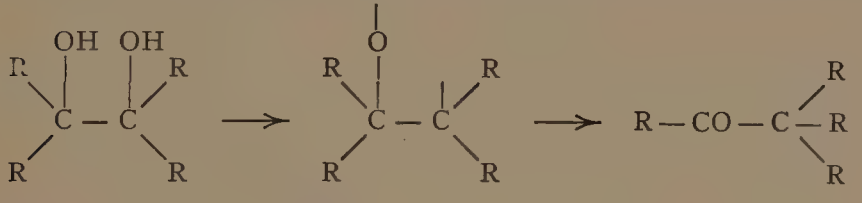
[11] Montagne, *Rec. trav. chim.*, **24**, 105 (1905); **25**, 413 (1906). See also Acree, *Am. Chem. J.*, **33**, 180 (1905); Klinger and Lonnes, *Ber.*, **29**, 2160 (1896); Zelinsky and Zelikow, *Ber.*, **34**, 3249 (1901); Meerwein, *Ann.*, **396**, 210 (1913).

ment of *para*-chlorotetraphenyl pinacol would take the following path:



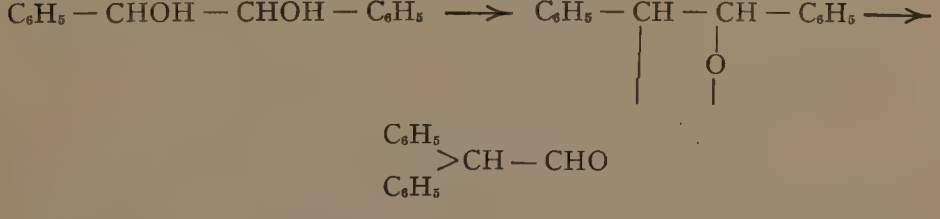
In the product actually obtained through the rearrangement, the chlorine is in the *para* position in each of the four rings.

Tiffeneau and his colleagues outline the reaction as follows:[12]



The possibility of attachment between oxygen and the unsaturated carbon is obvious. Tiffeneau, however, does not believe that such an ethylene oxide is formed in this reaction.

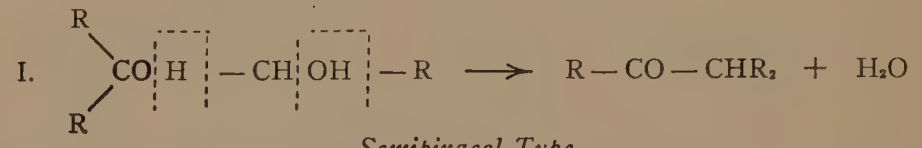
The rearrangement of a disecondary alcohol, such as hydrobenzoin, is represented by Tiffeneau in the same way.



In the case of 1, 2, glycols having one secondary and one tertiary alcoholic hydroxyl group, the rearrangements are classified

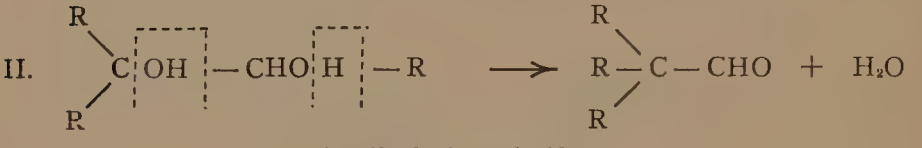
[12] Tiffeneau, *Bull. soc. chim.* (4), **1**, 1221 (1907); Tiffeneau and Orekhoff, *ibid.*, **33**, 195 (1923).

as semipinacol or semihydrobenzoin types, depending upon the direction in which the carbon radical migrates.[13]



Semipinacol Type

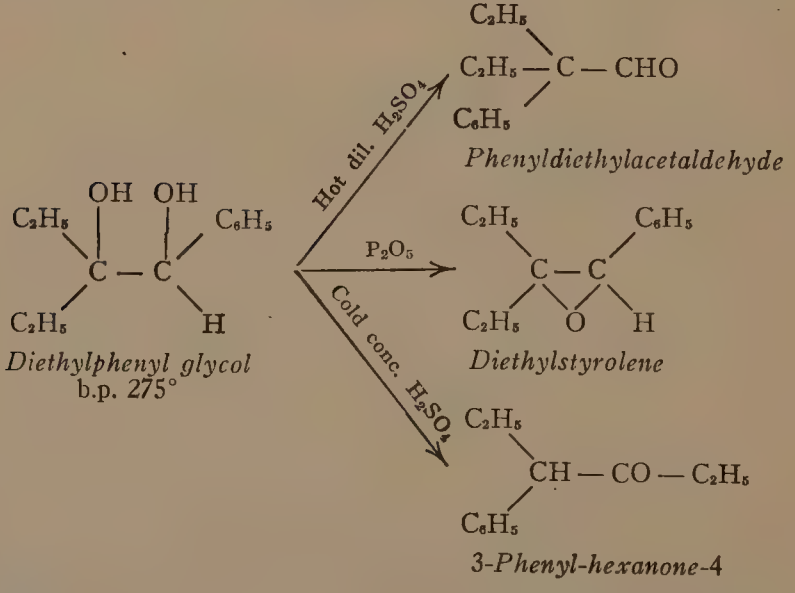
(OH removed from secondary alcohol group. Radical moves from tertiary to secondary carbon atom yielding a ketone.)



Semihydrobenzoin Type

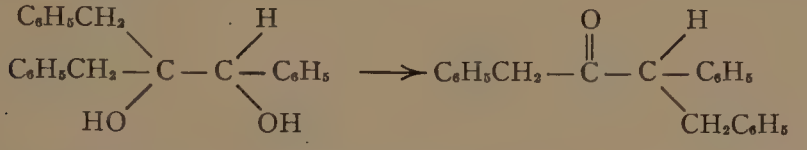
(OH removed from tertiary alcohol group. Radical moves from secondary to tertiary carbon atom yielding an aldehyde.)

The normal transposition in the aryldialkyl glycols of the type $R_2COH—CHOH—\phi$ gives rise to the aldehyde $R_2\phi C—CHO$. The aryl group, rather than an alkyl radical, is transposed under the influence of heat alone. In the presence of some dehydrating agents the semipinacolic transformation predominates. Tiffeneau reports the following results of experiments with diethylphenyl glycol.



[13] Tiffeneau and Lévy, *Bull. soc. chim.*, **33**, 735 (1923).

Similar results have been obtained with other glycols.[14] The difference in the action of dilute and of concentrated sulfuric acid, as indicated above, is not maintained through the series and many glycols decompose instead of rearranging when heated. Dibenzylphenyl glycol yields a ketone with either dilute or concentrated sulfuric acid.[15]



On the other hand, benzyldimethyl glycol yields 2-methyl-4-phenylbutanone-3.[16]

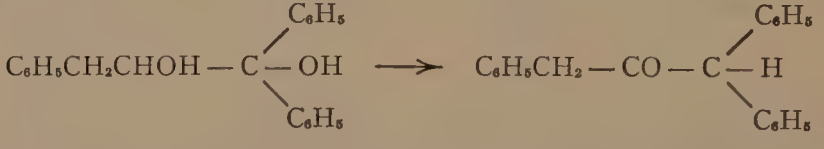
$$C_6H_5CH_2CHOH-COH(CH_3)_2 \longrightarrow C_6H_5CH_2-CO-CH(CH_3)_2$$

In unsymmetrical dimethyl-diethyl glycol an ethyl rather than a methyl group migrates.[17] Similarly propyl and isoamyl radicals seem to shift more readily than do methyl groups.[18] A systematic study of the dimethyldiethyl glycols by Nybergh [19] disclosed the fact that mixed pinacolones are always obtained, but the major part of the product is the pinacolone formed through the migration of the ethyl group. When the symmetrical pinacol was used the ratio between the two products was 4 : 1. The ratio was 20 : 1 when the unsymmetrical pinacol was isomerized. In each case the change was accomplished by treatment with cold concentrated sulfuric acid. In the cyclic series the anisyl and tolyl groups migrate in preference to the phenyl radical.[20] The determining factor, however, may not be a question of mobility of the alkyl radical but of relative stabilities of the two hydroxyl groups.[21] The stability of the hydroxyl group is modified by the radicals in its neighborhood.

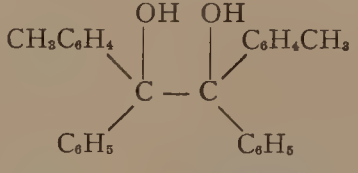
No invariable rule has been found that will justify a prediction as to the course a 1,2,glycol will follow in the process of rearrange-

[14] Orekoff and Tiffeneau, *Bull. soc. chim.*, **23**, 211 (1918).
[15] Orekhoff, *Bull. soc. chim.*, **25**, 113 (1919).
[16] Lévy, *Bull. soc. chim.*, **33**, 1655 (1923).
[17] Meerwein, *Ann.*, **396**, 200 (1913).
[18] Parry, *J. Chem. Soc.*, **107**, 108 (1915). On the other hand Locquin and Leers report that the methyl group is more mobile than *iso*-propyl or tertiarybutyl. *Bull. soc. chim.*, **39**, 655 (1926).
[19] Nybergh, *Ber.*, **55**, 1960 (1922).
[20] DeLaville, *Compt. rend.*, **184**, 462 (1927).
[21] Tiffeneau and Orekhoff, *Bull. soc. chim.*, **33**, 195 (1923).

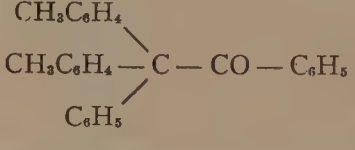
ment. The environment is often the determining factor. In cases of the hydrobenzoin type, where the change must result in the migration of either a hydrogen atom or an aryl group (the two being attached to the same carbon atom), it is always the aryl group that moves; but, unless the aryl group and the hydrogen atom are attached to the same carbon atom in the glycol, this rule does not always apply. Benzyldiphenyl glycol yields 1,1,3-triphenylpropanone-2.



That a tolyl group is more labile than the phenyl radical is indicated by the fact that *sym*-diphenylditolyl pinacol,

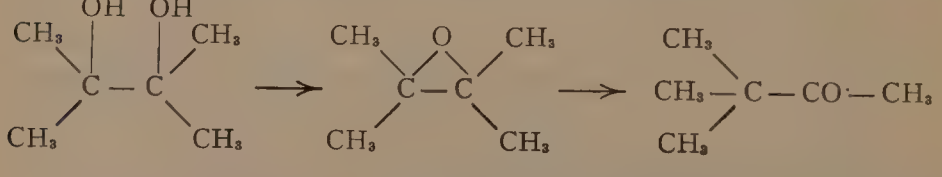


yields exclusively a ketone of the following structure:



On the other hand, the tendency of a phenyl radical to migrate is not modified by an *ortho* or a *para* substitution of chlorine or bromine.

The formation of ethylene oxide as an intermediate was assumed by Breuer and Zincke.[22] They wrote the reaction in this form:



In a few cases, as, for example, benzpinacol and *sym*-diphenylditolyl glycol, the oxides had been isolated.[23] When they were subjected to the treatment that converts the free pinacols into

[22] Breuer and Zincke, *Ann.*, **198**, 148 (1879).
[23] Thoerner and Zincke, *Ber.*, **29**, 2158 (1896); **10**, 1477 (1877); **11**, 68 (1878); **16**, 400 (1882).

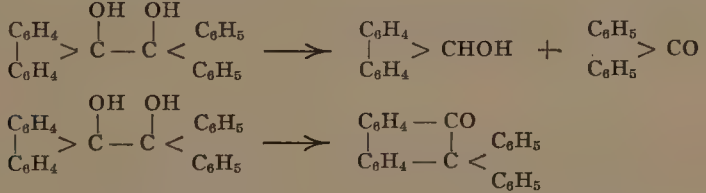
pinacolones these oxides yielded the same products. This mechanism, however, cannot be general, for in some cases it is more difficult to convert the ethylene oxide into an aldehyde or ketone than it is to change the corresponding glycol into the same product. Moreover, the pinacols and their anhydrides do not always yield the same products.[24] From diphenyldiphenylene glycol Meerwein obtained diphenylphenanthrone through migration of the phenylene group. This resulted in an expansion of the ring. From the corresponding ethylene oxide he obtained phenylbenzoyl fluorene through migration of a phenyl group. The experiments, however, were not performed under similar conditions.[25]

The crucial test of this theory was made by comparing the rates of transformation of a pinacol and of the corresponding ethylene oxide. It was found in the case of tetrachlorobenzpinacol and the corresponding oxide that the latter, when treated with acetyl chloride, reacts more slowly than the former.[26] Each reaction follows the unimolecular law. Apparently, then, the rate of rearrangement was measured in the first instance and the rate of hydrolysis of the oxide in the second.[27]

[24] Meerwein, *Ann.*, **396**, 200 (1913).

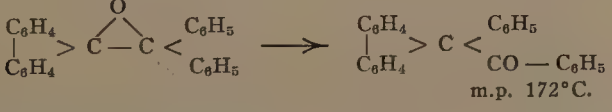
[25] The pinacol was dissolved in cold concentrated sulfuric acid. The ethylene oxide was formed in the oxidation of diphenyldiphenylene ethylene by chromic acid. It was not isolated. The ketone, phenylbenzoyl fluorene, appeared as the final product.

When heated alone to 200°C. the pinacol decomposes as follows:



m.p. 162°C. m.p. 197°C.

The ethylene oxide reaction is represented by the equation:



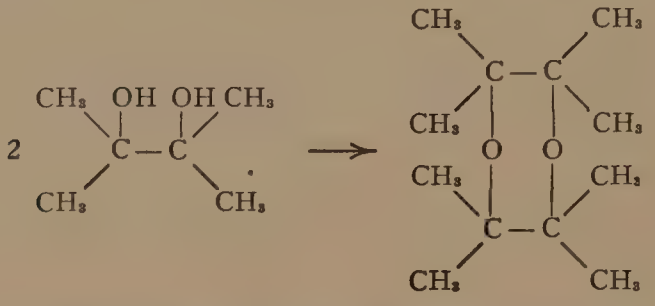
m.p. 172°C.

[26] Meerburg, *Rec. trav. chim.*, **24**, 131 (1905); Montagne, *ibid.*, **24**, 105 (1905); **28**, 272 (1909).

[27] A different result was obtained by Krassusky (Abstr. *Liebig's Jahresber.*, **55**, 783 (1902)) who reports that α-alkylene oxides, in the presence of zinc chloride, are converted into aldehydes or ketones at lower temperatures than the temperatures required to make the same products from the corresponding glycols.

It was suggested by Faworsky [28] that a dialkylene oxide might represent an intermediate stage in the pinacol change.

The preliminary step would be a dehydration of the following type:



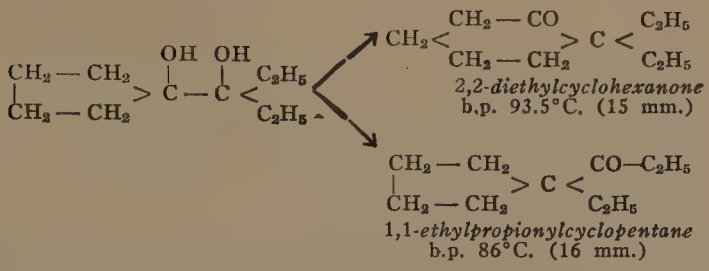
The idea was based upon the actual production of diethylene oxide when a mixture of twenty-five parts of ethylene glycol and one part of concentrated sulfuric acid was distilled. This view is not tenable for the rearrangement can be accomplished in aqueous solutions that would hydrolyze the oxide. Moreover, when tetramethyl pinacol is distilled with a small amount of concentrated sulfuric acid—a condition favorable to the production of the dialkylene oxide—the product formed is not the oxide nor the pinacolone but the unsaturated hydrocarbon dimethylbutadiene.[29]

Meerwein, like Tiffeneau and Montagne, held the opinion that the elimination of water is the first step in a pinacol rearrangement and that the water is derived from the two hydroxyl groups. He agreed with them also in the conclusion that the rearrangement follows dehydration with such speed that the ethylene oxide has no chance to form.

Of the many methods available for converting a pinacol into a pinacolone Meerwein preferred treatment with cold concentrated sulfuric acid. The details of one experiment will indicate his technique.

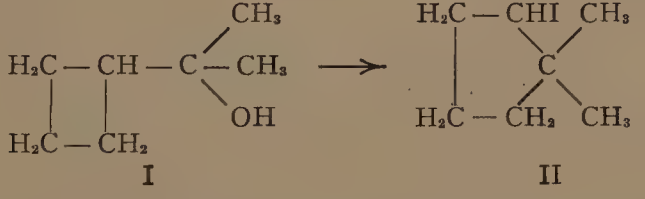
Ninety grams of liquid diethyltetramethylene glycol was poured with constant stirring into 720 grams of concentrated sulfuric acid which had been cooled to — 10°C. The glycol dissolved imparting a yellow color to the acid. After standing for two hours the solution was poured on ice and the pinacolone was separated from the mixture by distillation with steam. Two products were obtained.

[28] Faworsky, *Chem. Zentr.*, **1907**, I, 15.
[29] Bayer and Co., *Chem. Zentr.*, **1912**, II, 1757.



To separate them semicarbazide was added and the mixture was allowed to stand at room temperature for two days. The semicarbazone of the cyclohexanone derivative (m.p. 203°C.) was crystallized from hot alcohol. The semicarbazone of the cyclopentane derivative (m.p. 148.5°C.) was obtained in crystalline form by diluting the alcohol with water. They were further purified by recrystallizing from alcohol, ligroin or ether. The free ketones were obtained from the semicarbazones by warming the latter with dilute sulfuric acid.

In many cyclic compounds an expansion of the ring is accomplished through the pinacol reaction.[30] Cyclobutyldimethyl carbinol, I, is changed by hydrogen iodide to 1,1-dimethyl-2-iodocyclopentane, II. Hydrogen bromide produces the corresponding bromine derivative.



I II

Not all pinacols are changed to pinacolones with equal ease. In general the aromatic compounds require treatment with more concentrated acids than are used in connection with aliphatic pinacols. Tetramethyl pinacol rearranges at 100° C. in the presence of 5% oxalic acid [31] or by heat alone at a higher temperature.

Michael specifies three factors that determine the course of the rearrangement. (1) The relative ease of the elimination of water in the various possible ways, (2) the energy requirements in the separation of the radicals capable of migrating, (3) the heats of formation of the possible rearrangement products. In consideration of these factors he reaches the conclusion that the glycols do not all follow the same path in the process of rearrangement. The possible mechanisms by which water may be removed from an α,β-glycol containing a primary or a secondary alcoholic group are as follows:

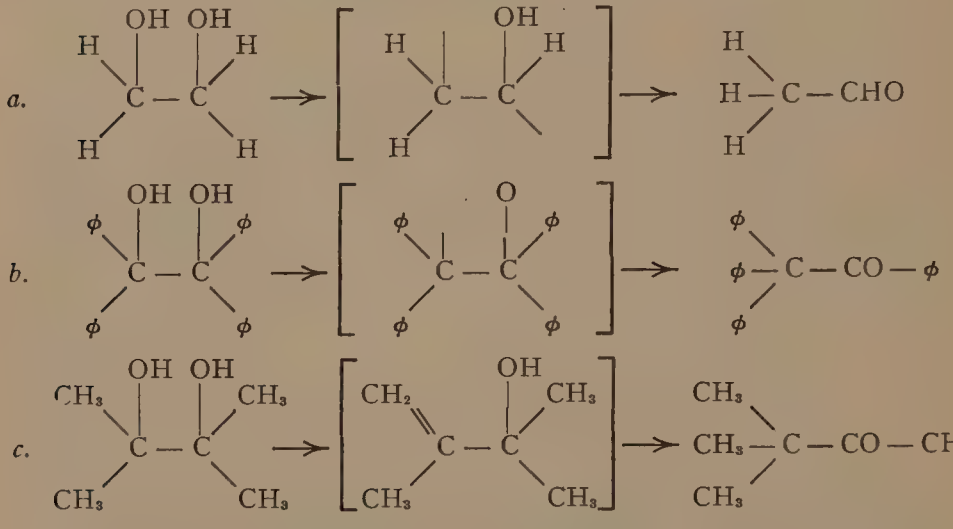
[30] Kizhner, *J. Russ. Phys. Chem. Soc.*, **40**, 994 (1908).
[31] Vorländer, *Ber.*, **30**, 2266 (1897).

(*a*) Water is eliminated through the hydroxyl attached to the *α* carbon atom with nuclear hydrogen attached to the *β* carbon atom.

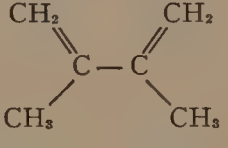
(*b*) Water is eliminated through the two hydroxyl groups.

(*c*) Water is eliminated through the union of one hydroxyl group with hydrogen in an adjacent alkyl radical.

In the pinacols plan (*a*) is structurally impossible. Michael believes that the simple glycols and their symmetrical dialkyl derivatives follow path (*a*). Plan (*b*) he applies to the aromatic pinacols and plan (*c*) to the aliphatic pinacols.



More complete dehydration of the pinacol under this plan (*c*) would yield dimethylbutadiene



This hydrocarbon is actually obtained from pinacol by distillation with a small quantity of concentrated sulfuric acid and it is converted into pinacolone by dilute sulfuric acid.

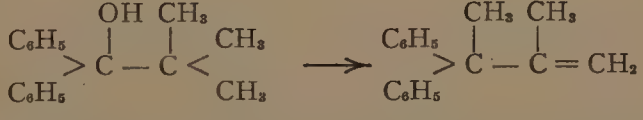
In this connection Michael says:

"A factor, decidedly conducive to the dehydration through the two hydroxyl groups of these glycols (Type *b*), is the property of aryl radicals to favor the substitution reactivity of the hydroxyl group in aryl substituted methyl alcohols, i.e., to lessen the expenditure of energy required to separate it from the hydrocarbyl radical. They not only exert this influence to a far greater degree than any alkyl radical, but it increases in

extent with the relative positive influence of the aryl group on the carbinol carbon atom.[32] Further, the aryl more than the alkyl radical is susceptible to a shifting in the molecule, since it decreases the affinity of carbon to carbon to a greater degree, and this influence, too, is augmented with increasing positivity.[33] These relations manifest themselves, for instance, in the quantitative breaking down of benzopinacol at its melting point (204°C.) into benzophenone and diphenylcarbinol;[34] in the migration of the aromatic, and not the aliphatic, radical in the transformations of mixed pinacols;[35] and that the more positive of the aryl groups[36] shifts its position in the molecule in a pinacol rearrangement.[37] The intramolecular elimination of water in the *sym*-diaryl-glycols tends, therefore, to proceed through the two hydroxyl groups, while the loss of water in the *sym*-dialkyl derivatives occurs through the utilization of a nuclear hydrogen atom and a hydroxyl group. The hindrance to the migration of the hydrocarbyl radical is less in the aromatic derivatives. These two factors unite to cause the characteristic difference in the behavior of the *sym*-diaryl- and dialkyl-α,β-glycols. The aromatic substances yield diaryl-acetaldehydes, by aryl migration, while the latter class of compounds gives ketones. It is evident now why the structural change takes place more readily with ditolyl-diphenyl than with tetraphenyl-glycol, and why the more positive tolyl radical in the mixed glycol is the migrating group."

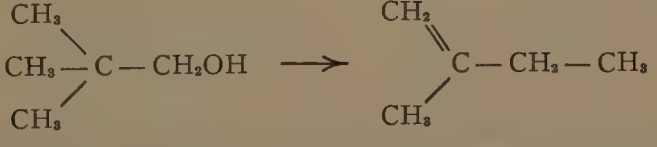
The structural modification that sometimes occurs when a monohydric tertiary alcohol is dehydrated is known as the Wagner rearrangement.[38]

When diphenyl-tertiarybutyl carbinol is warmed with a dehydrating agent it is converted into 3,3-diphenyl-2-methyl-butene-1.



The structure of this unsaturated hydrocarbon was established by Bateman and Marvel.[39]

Similarly, tertiarybutylcarbinol is converted into 2-methyl-butene-1.

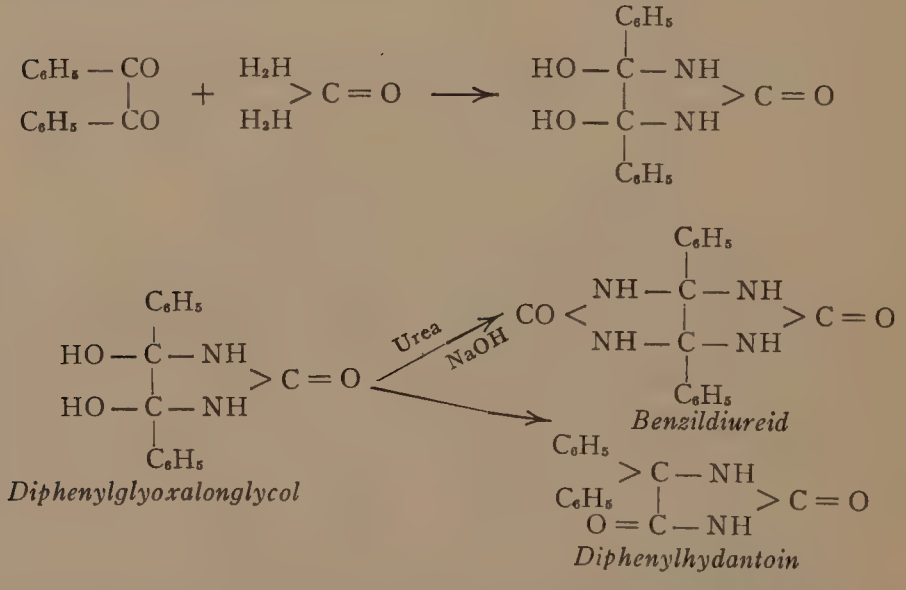


[32] Michael, *J. Am. Chem. Soc.*, **32**, 991 (1910). Meerwein, *loc. cit.*, 221-224.
[33] Auwers, *Ber.*, **24**, 1776 (1891).
[34] Thoerner and Zincke, *Ber.*, **10**, 1474 (1877).
[35] Tiffeneau, *Ann. chim. phys.* (8), **10**, 322 (1907); Parry, *J. Chem. Soc.*, **107**, 108 (1915).
[36] Michael, *loc. cit.*
[37] Acree, *Am. Chem. J.*, **33**, 180 (1905).
[38] Wagner and Brykner, *Ber.*, **32**, 2302 (1899).
[39] Bateman and Marvel, Detroit Meeting, Am. Chem. Soc., 1927.

It is not known whether the transposition precedes the dehydration or if a trimethylene ring is formed by loss of water as an intermediate product. The latter scheme is supported by Ruzicka and Liebel.[40] The conversion of borneol or of isoborneol into camphene is another example of the Wagner transposition.[41]

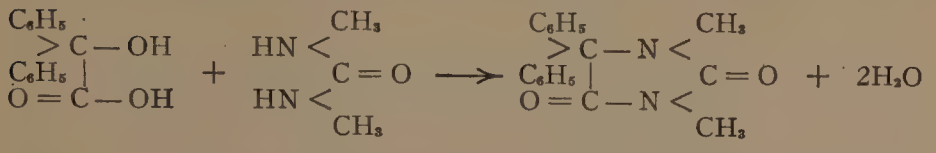
Robinson has made an attempt to formulate a mechanism which is applicable to the rearrangement of a monohydric tertiary alcohol and to ditertiary alcohols as well.[42] It involves the use of partial valence bonds and the formation of cyclic intermediates that cannot be isolated. It therefore lacks direct experimental verification, but has been applied with some success to several reactions.

The conversion of diphenylglyoxalon glycol into diphenylhydantoin is an example of the pinacol rearrangement in cyclic compounds.[43] Benzil combines with urea to form this glycol. When condensation takes place in the absence of alkali the glycol reacts with a second molecule of urea. In the presence of a base rearrangement occurs.

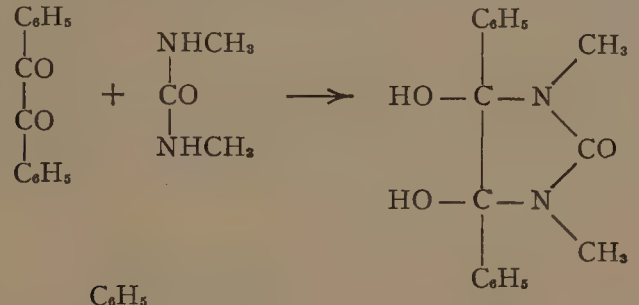


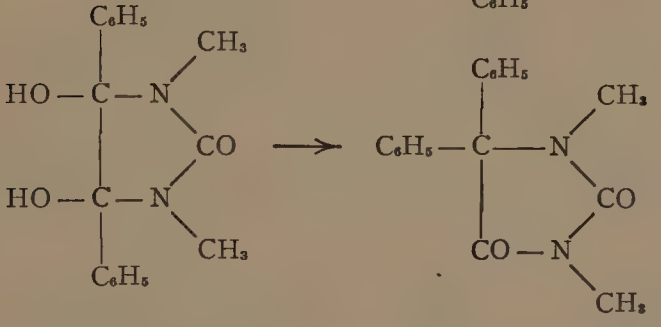
When benzilic acid is melted with symmetrical dimethyl urea water is eliminated and 1,3-dimethyl-5,5-diphenyl hydantoin is formed.

[40] Ruzicka and Liebel, *Helv. Chim. Acta.*, **6**, 267 (1923).
[41] Rusicka, *Helv. Chim. Acta.*, **1**, 110 (1918); Wallach, *Ann.*, **230**, 233 (1885); Wagner and Brykner, *Ber.*, **33**, 2121 (1900).
[42] Robinson, *Mem. Manchester Lit. and Phil. Soc.*, **64**, 1 (1920).
[43] Biltz, *Ber.*, **40**, 4806 (1907); **41**, 1379 (1908).

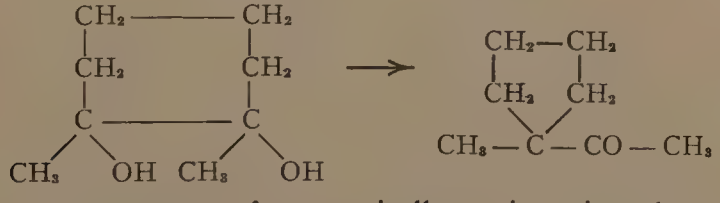


The same product is formed from benzil and symmetrical dimethyl urea, the process obviously involving a pinacol rearrangement.



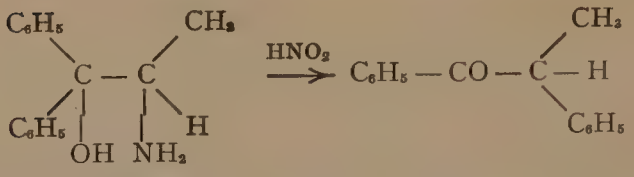


There are many other examples of the pinacol rearrangement in cyclic compounds.[44] Some of these reactions result in an expansion of the ring, others give rise to smaller cyclic structures and still others leave the ring unaltered. The glycol 1,2,-dimethyl-cyclohexandiol-1,2 is converted by dilute sulfuric acid or by heat alone (180° C.) into a cyclopentane derivative.[45]



The rearrangement of an optically active pinacol can occur without racemization. This possibility is indicated by the conversion of *laevo*-β-amino-$\alpha\alpha$-diphenyl-*n*-propyl alcohol into *dextro*-phenylmethylacetophenone.[46]

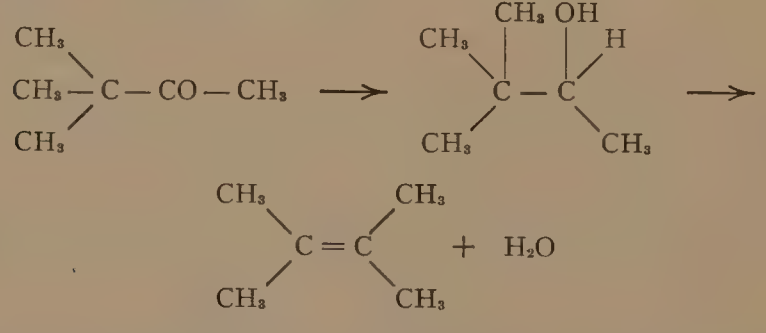
[44] Meiser, *Ber.*, **32**, 2049 (1899); Meerwein and Unkel, *Ann.*, **376**, 152 (1910).
[45] Nametkin and Delektorsky, *Ber.*, **57**, 583 (1924).
[46] McKenzie, Rogers and Wills, *J. Chem. Soc.*, **129**, 779 (1926).



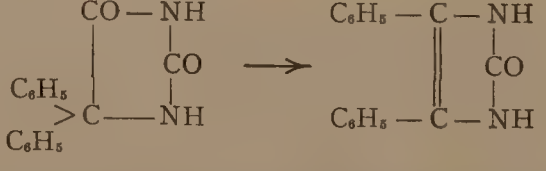
It is suggested by McKenzie, Rogers and Wills that the retention of asymmetry is due to the presence of an electric charge on the carbon atom during the interval between the elimination of water and the migration of the phenyl radical. The theory that a positive charge may act like an atom in establishing asymmetry has been advanced by others.[47]

REVERSED PINACOL REARRANGEMENTS

By means of reducing agents it is sometimes possible to convert unsymmetrical ketones into symmetrical derivatives of ethylene. The process involves the migration of a carbon radical and either that of a hydrogen atom or of a hydroxyl group with subsequent or concomitant loss of water. Thus methyl-triphenylmethyl ketone is reduced to tetramethyl ethylene.

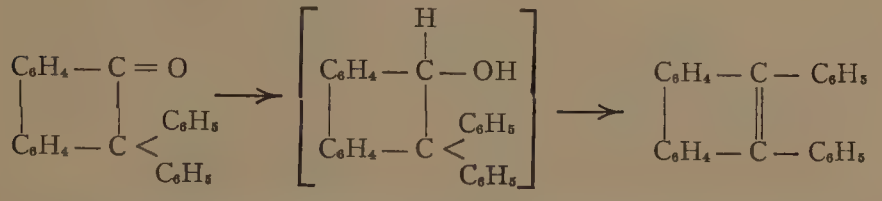


Similarly phenyltriphenylmethyl ketone, when reduced by phosphorus and hydrogen iodide yields symmetrical tetraphenylethylene, and 5, 5-diphenylhydantoin under the same treatment yields 4,5-diphenyl glyoxalone.[48]

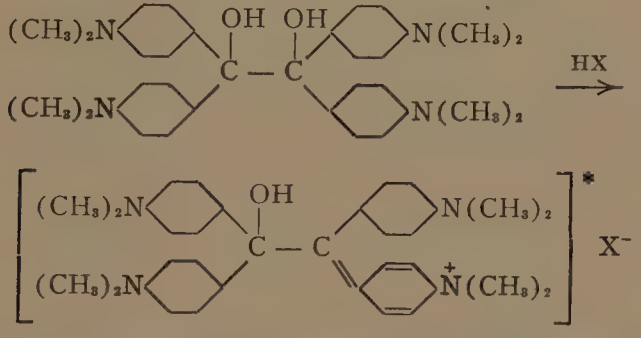


[47] Bülmann, *Ann.*, **388**, 330 (1912); Holmberg. *Ber.*, **59**, 1569 (1926).
[48] Biltz and Seydel, *Ber.*, **46**, 138 (1913); Biltz, *Ann.*, **368**, 164 (1909). See also Brunner, *Monatsh.*, **17**, 276 (1896); Baeyer, *Ber.*, **32**, 2429 (1899); Wolff, *Ann.*, **322**, 351 (1902); Knorr, *Ber.*, **36**, 1272 (1903).

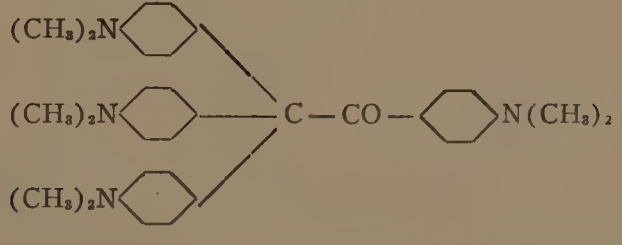
When 9,9-diphenylphenanthrone is distilled with zinc dust it is converted into 9,10-diphenylphenanthrene.[49]



A remarkable case of retropinacol rearrangement has been reported by Madelung and Oberwegner.[50] Octamethyltetraaminotetraphenyl pinacol forms a dye salt with one equivalent of an acid.



When the free pinacol is refluxed with absolute alcohol or the dye salt is heated with a mixture of water and alcohol containing sodium acetate a pinacolone is formed. The latter has the structure



This is a direct pinacol rearrangement. It is claimed that, when this pinacolone is heated with acetic acid or when an alcoholic solution of it is heated with one equivalent of a mineral acid, the monoacid dye salt is regenerated.

[49] Werner and Grob, *Ber.*, **37**, 2903 (1904); Acree, *Am. Chem. J.*, **33**, 183 (1905).

[50] Madelung and Oberwegner, *Ber.*, **60**, 2469 (1927).

* The authors do not use the quinoid structure in their paper. The formula is presented in the quinoid form here in conformity with the plan followed throughout this book.

BENZIL

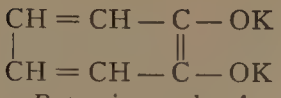
A rapid, irreversible and almost quantitative conversion of benzil into benzilic acid is accomplished when the former is warmed with an aqueous solution of a base.

$$C_6H_5-CO-CO-C_6H_5 + KOH \longrightarrow \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!>COH-COOK$$

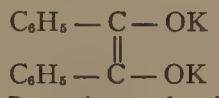
The addition of water or of a base has always been considered the first step in this rearrangement.[51] A blue-violet color generally appears when benzil is treated with an alkali and Scheuing at one time regarded the colored compound as an intermediate product. He abandoned this view when he found it possible to convert benzil into benzilic acid, without the development of color, through the agency of potassium methylate.[52] Scheuing presented evidence that only one molecule of water, or of metallic hydroxide, or of an alcoholate, adds to benzil when the reaction occurs in aqueous or in alcoholic solution. This, however, was established at an earlier date [53] and has been confirmed by others. At low temperatures (10° C.) the compound $\phi-C(ONa)(OR)-CO-\phi$ formed in pyridin solutions, can be isolated. At higher temperatures according to Scheuing, the rearrangement occurs. Lachman, on the other hand, reports that in anhydrous solvents no rearrangement of this addition product occurs. When allowed to stand at room temperature in these solvents he found that this addition product yields one mol of benzaldehyde and one mol of benzoic ester.

A dipotassium derivative of benzil is obtained by treatment with metallic potassium in benzene or in liquid ammonia.[54] The product has been identified as the potassium salt of dihydroxystilbene.[55] It is a very reactive compound, yet capable of independent existence. The activity of the salts of polyhydric phenols may be due to their somewhat similar structures.

[51] Erlenmeyer, *Ann.*, **316**, 83 (1901).
[52] Scheuing, *Ber.*, **56**, 252 (1923).
[53] Acree, *Am. Chem. J.*, **33**, 180 (1905).
[54] Staudinger and Binkert, *Helv. Chim. Acta.*, **5**, 703 (1922).
[55] Dihydroxystilbene or stilbene glycol is not known in the free state. Its esters, however, are stable compounds. In many cases benzoin acts as if it were an unsaturated glycol having this structure.



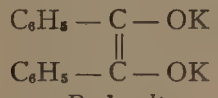
Potassium salt of pyrocatechol



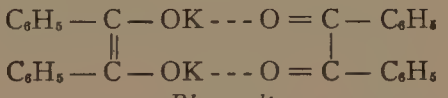
Potassium salt of stilbene glycol

The blue violet color that has been described by many observers [56] appears when one equivalent of potassium has been added to a benzene solution of benzil. A red compound is formed when two equivalents of the metal have been taken up by the diketone. The reaction proceeds rapidly at the boiling point of the solvent. It is a reversible process. The red changes to blue upon the addition of benzil and the blue salt is converted into the red one by the addition of potassium. Oxidation is avoided by preparing these salts in an atmosphere of nitrogen.

The red compound, according to Staudinger and Binkert, is the dipotassium salt of stilbene glycol, and the blue compound is a quinhydrol composed of one molecule of the red derivative and one of benzil.

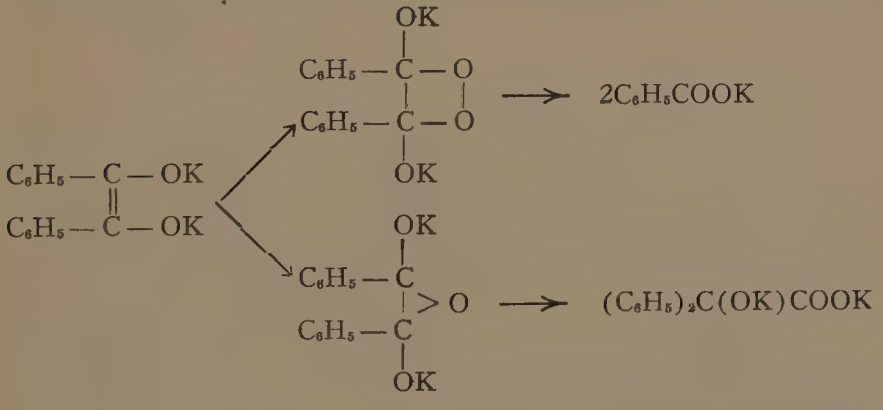


Red salt



Blue salt

When oxygen or air is bubbled through a warm solution of the red salt the color changes to violet and the violet color finally disappears as a mixture of benzilic and benzoic acids precipitates. Staudinger formulates the reaction as follows:

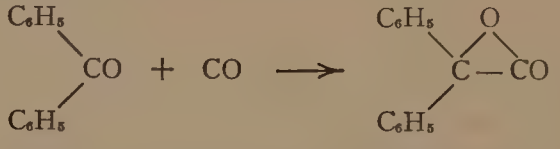


He suggests that the conversion of benzil to benzilic acid by aqueous alkali may be accomplished through a similar mechanism.

[56] Beckmann and Paul, *Ann.*, **266**, 1 (1891); Schlenk and Thal, *Ber.*, **46**, 2850 (1913); Nef, *Ann.*, **308**, 264 (1899).

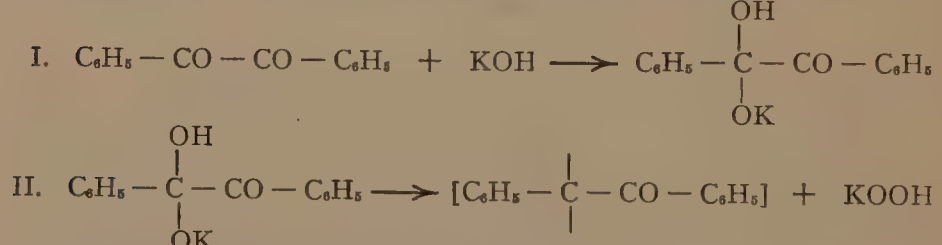
The addition of one molecule of base to each of the carbonyl groups with subsequent elimination of water would result in the formation of an ethylene oxide. A similar suggestion was made by Tiffeneau,[57] who likewise was cautious enough to admit that the mechanism is hypothetical and not susceptible to direct experimental verification.

Nef assumed the preliminary addition of water to benzil and subsequent dissociation of the addition compound into benzophenone and dihydroxymethylene. The latter, after rearranging to formic acid, was said to combine with the benzophenone to form benzilic acid.[58] A more highly speculative and improbable mechanism could hardly be imagined. That the reaction does not follow this path has been definitely established.[59] Nef also speculated on the possibility of the dissociation of benzil into carbon monoxide and benzophenone.[60] These products, he assumed, would recombine to form a lactone.



By hydrolysis this was believed to yield benzilic acid. The theory was refuted by Acree who showed that carbon monoxide and benzophenone when heated with alkali fail to yield these products.[61]

The formation of diphenylketene as an intermediate has been proposed.[62] The following steps are involved in this scheme:



Formulas written within parentheses represent purely hypothetical substances.

[57] Tiffeneau, *Rev. gén. sci.*, **18**, 583 (1907).
[58] Nef, *Ann.*, **298**, 202 (1897).
[59] Klinger and Standke, *Ber.*, **22**, 1211 (1889); Lachman, *J. Am. Chem. Soc.*, **44**, 335 (1922).
[60] Nef, *Ann.*, **335**, 272 (1904).
[61] Acree, *Am. Chem. J.*, **33**, 180 (1905).
[62] Schroeter, *Ber.*, **42**, 2336 (1909).

III. $[C_6H_5 - \overset{|}{\underset{|}{C}} - CO - C_6H_5] \longrightarrow \begin{matrix} C_6H_5 \\ \\ C_6H_5 \end{matrix} > C = CO$

IV. $\begin{matrix} C_6H_5 \\ \\ C_6H_5 \end{matrix} > C = CO + KOOH \longrightarrow \begin{matrix} C_6H_5 \\ \\ C_5H_6 \end{matrix} > COH - COOK$

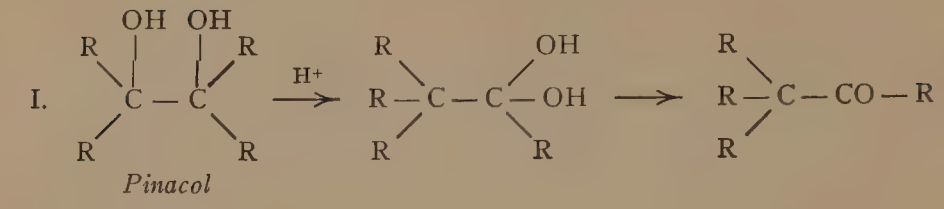
This mechanism has been studied critically. The theory advanced by Schroeter involves the assumption that in the presence of water or of alcohol the addition of hydrogen peroxide, or of its potassium salt, to diphenylketene is so much more rapid than the hydrolysis or the alcoholysis of the ketene that an almost quantitative yield of benzilic acid is obtained. Nicolet and Pelc tested this possibility.

"Molecular quantities of the ketene and peroxide solutions were mixed and allowed to stand for lengths of time varying from one hour to eight months. In all cases unchanged hydrogen peroxide was still present. The solutions were worked up by treatment with water or aqueous alkali, and the melting points of the liberated acids determined. In every case benzilic acid was present, as indicated by the melting points, and this was confirmed by actually isolating it; but the amount was no greater than when the ketene itself, without the addition of peroxide, was treated in the same way. Prolonged contact of the two substances also gave no increase in the yield of benzilic acid." [63]

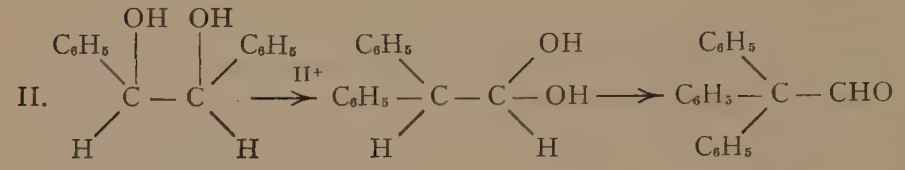
Tiffeneau assumes the addition of water to each of the carbonyl groups and from that point on applies the mechanism which he developed in connection with the pinacol rearrangement.[64] Michael [65] claims that the driving force in the reaction is "the great positive energy of the alkali," but Lachman succeeded in obtaining weighable quantities of benzilic acid by heating benzil with water in the absence of alkali.

As envisaged by Lachman, elimination of water is the last step in this and in all related changes. He believes that the rearrangement begins with the migration of a hydroxyl group. Concomitant with this transfer, or immediately following it, either hydrogen or a carbon radical moves in the opposite direction (*metakliny*).[66] The application of this view to a group of related rearrangements is shown below. In these equations the shifts of hydroxyl and of the radical H, R or C_6H_5 are represented as simultaneous processes preceding the elimination of water.

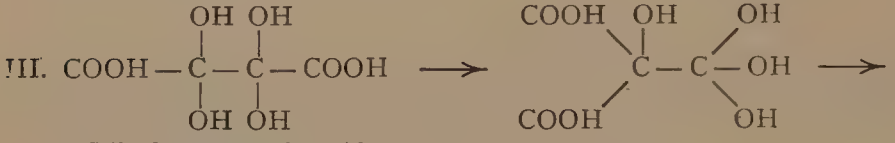
[63] Nicolet and J. J. Pelc, *J. Am. Chem. Soc.*, **43**, 935 (1921).
[64] Tiffeneau, *Rev. gén. sci.*, **18**, 584 (1907).
[65] Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920).
[66] Lachman, *J. Am. Chem. Soc.*, **44**, 336 (1922); **45**, 1511 (1923); **46**, 779 (1924).



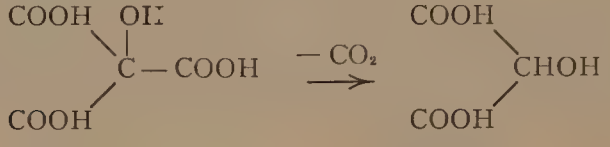
Pinacol

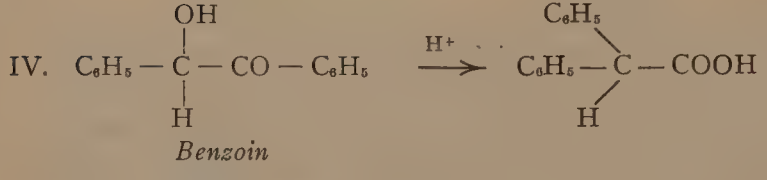


Hydrobenzoin

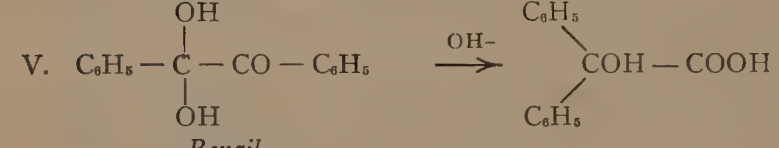


Dihydroxytartaric acid





Benzoin



Benzil
(hydrated)

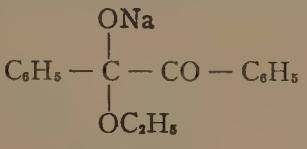
With reference to the migration of a hydroxyl group Lachman says:

"The assumption of a mobile hydroxyl group is not new. Lieben was among the first to suggest it for the pinacol rearrangement.[67] There seems, however, to have existed a strong prejudice against the assumption of mobility for anything except hydrogen. Michael, in his recent critique, did not mention Lieben's hypothesis. Tiffeneau dismissed it somewhat satirically.[68] Meerwein,[69] whose recent work has brought out evidence strongly

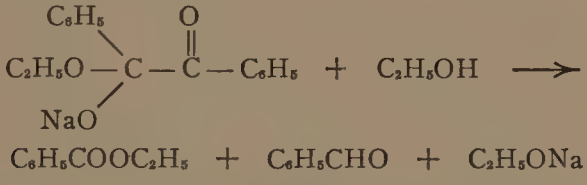
[67] Lieben, *Monatsh.*, **23**, 63 (1902).
[68] Tiffeneau's phrase is "une sorte de chassé-croisé."
[69] Meerwein, *Ann.*, **396**, 200 (1913); *ibid.*, **419**, 121 (1919).

corroborative of the views here set forth, gave it some thought, but could not find in it a sufficient degree of 'Notwendigkeit' and therefore adopted the view of Tiffeneau."

In support of this theory we have the fact that benzil does not rearrange under conditions that preclude the existence of hydroxyl groups in the intermediate product.[70] Thus benzil reacts with sodium ethylate, forming the addition product



but neither the NaO— nor the C_2H_5O— is capable of migrating. In absolute alcohol, or in an anhydrous mixture of ether and alcohol, this compound decomposes with the production of ethyl benzoate and benzaldehyde.



The cleavage is almost quantitative. On the other hand, in the presence of water (20% or more) the rearrangement to benzilic acid is nearly quantitative. Lachman attributes this influence of the solvent to the mobility of the OH group. In the presence of water the ONa group is hydrolyzed and the rearrangement becomes possible.

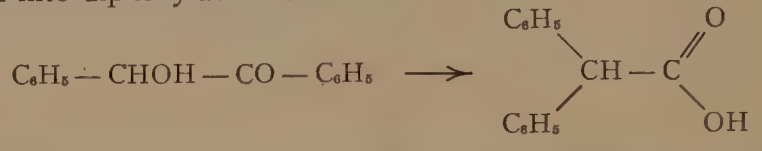
Potassium cyanide acts upon an alcoholic solution of benzil, rupturing the diketone with the formation of ethyl benzoate and benzaldehyde.[71] If benzoyl cyanide is the first product formed it is immediately converted into the ester for the reaction is completed within a few minutes. This accounts for the results obtained by Michael and Palmer,[72] who dissolved benzil in alcohol, added potassium cyanide, heated until the latter had dissolved and finally acidified with hydrochloric acid. They obtained ethyl benzoate and benzaldehyde and attributed the result to the action of hydrocyanic acid. If they had analyzed the mixture after dissolving the

[70] Lachman, *J. Am. Chem. Soc.*, **46**, 779 (1924).
[71] Jourdan, *Ber.*, **16**, 659 (1883); Lachman, *J. Am. Chem. Soc.*, **45**, 1522 (1923).
[72] Michael and Palmer, *Am. Chem. J.*, **7**, 190 (1885).

potassium cyanide and before acidifying they probably would have found the same products. The reaction, no doubt, was finished before hydrocyanic was released in the solution.

BENZOIN

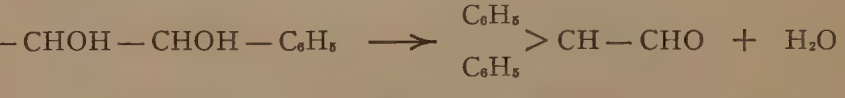
When heated to 250° C. with 3*M*. sulfuric acid, benzoin is converted into diphenylacetic acid.[73]



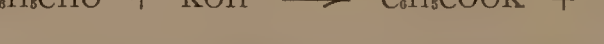
Not more than a ten per cent yield can be obtained. At the high temperature required to cause this change other reactions predominate.

HYDROBENZOIN

The glycol, hydrobenzoin, gives a good yield of diphenylacetaldehyde when warmed with sulfuric acid.[74]



It will be observed that benzil adds water in rearranging, benzoin rearranges without loss or gain of water, and hydrobenzoin loses water in the process. In each case one carbon atom is oxidized and an adjacent carbon atom is reduced. In all rearrangements of glycols an intramolecular oxidation and reduction occurs and a similar generalization can be made with reference to the rearrangements of oximes and of amides. This fact establishes a relationship between the rearrangement of a glycol and the Cannizzaro[75] reaction which is a case of intermolecular oxidation and reduction.



When 9,10-dihydroxystearic acid is fused with potassium hydroxide the principal product is the potassium salt of α-hydroxy-

[73] Lachman, *J. Am. Chem. Soc.*, **45**, 1529 (1923).
[74] Breuer and Zincke, *Ann.*, **198**, 141 (1879).
[75] Cannizzaro, *Ann.*, **88**, 129 (1853); Lachman, *J. Am. Chem. Soc.*, **45**, 1531 (1923).

α-octyl-sebacic acid.[76] This is most easily explained by assuming the hydrobenzoin type of rearrangement followed by an oxidation.

$$CH_3(CH_2)_7\,CHOH\,CHOH(CH_2)_7\,COOH \xrightarrow{3KOH\ +\ O_2}$$

$$CH_3(CH_2)_7\,C(OK)(COOK)(CH_2)_7COOK + 4H_2O$$

The corresponding diketostearic acid,

$$CH_3(CH_2)_7CO-CO-(CH_2)_7COOH,$$

when heated to 160° C. with potassium hydroxide is converted partly into α-hydroxy-α-octyl-sebacic acid through the benzil type of rearrangement and partly into dihydroxystearic acid, pelargonic acid and azelaic acid through a modified Cannizzaro reaction.[77]

As a rule a 1,2-diketone having a methylene group adjacent to each of the carbonyl groups will not respond to the benzil rearrangement. This was shown by von Pechmann[78] in his study of diacetyl and its homologues.

The conversion of dihydroxytartaric acid into tartronic acid by the action of alkali or by heat alone is a change of the benzil-benzilic acid type. Dihydroxytartaric acid has the formula $COOH-C(OH)_2-C(OH)_2-COOH$. It is often written $COOH-CO-CO-COOH$, but the free acid and its salts actually contain water enough to justify the former structure. Heat converts this acid into tartronic acid and carbonic acid. The reaction may be represented as follows:

$$COOH-C(OH)_2-C(OH)_2-COOH \longrightarrow$$

$$C(COOH)(OH)(COOH) + H_2O$$

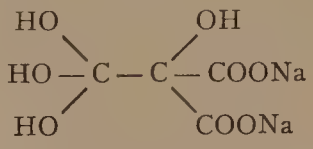
The tricarboxylic acid then yields tartronic acid,

$$COOH-CHOH-COOH,$$

and carbon dioxide. The sodium salt of dihydroxytartaric acid rearranges in the same way. Lachman formulates the reaction as follows:

[76] Le Sueur, *J. Chem. Soc.*, **79**, 1313 (1901).
[77] Nicolet and Jurist, *J. Am. Chem. Soc.*, **44**, 1136 (1922).
[78] von Pechmann, *Ber.*, **21**, 1411 (1888).

$$\mathrm{COONa-C(OH)_2-C(OH)_2-COONa} \longrightarrow$$



and he remarks, "We can thus understand why this salt loses carbon dioxide and water simultaneously when it is carefully heated. The carbon dioxide comes from the newly formed ortho-carboxyl group, $-C(OH)_3$, not from the preexisting neutralized groups." [79]

Danilov reports the conversion of diphenylglycol aldehyde into benzoin by heating an alcoholic solution of the aldehyde with a few drops of sulfuric acid.[80]

$$(C_6H_5)_2COH-CHO \longrightarrow C_6H_5-CHOH-CO-C_6H_5$$

He claims also that benzil is produced when diphenylglycol aldehyde is oxidized by an alkaline solution of copper sulfate.

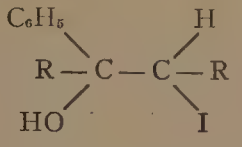
$$(C_6H_5)_2COH-CHO \xrightarrow{\frac{1}{2}O_2} C_6H_5-CO-CO-C_6H_5 + H_2O$$

This is virtually a reversal of the benzil-benzilic acid rearrangement and a most unexpected result. The immediate oxidation of the aldehyde group to carboxyl would be the most probable reaction. But this would give rise to benzilic acid and the latter certainly will not revert to benzil in an alkaline medium. The only remaining course for the reaction seems to be a rearrangement of the aldehyde to benzoin and subsequent oxidation of this product to benzil. The difficulty with this explanation lies in the fact that when benzil is warmed with an alkali it is rapidly converted into benzilic acid. Yet Danilov recovered 0.4 gram of benzil and only 0.1 gram of benzilic acid after one gram of an alcoholic solution of diphenylglycol aldehyde had been heated to 80° C. for twelve hours with copper sulfate and an excess of potassium hydroxide.[81]

IODOHYDROLS

Closely related to the hydrobenzoin rearrangement is the transformation of iodohydrols of the type

[79] Lachman, *J. Am. Chem. Soc.*, **43**, 2091 (1921).
[80] Danilov, *Ber.*, **60**, 2390 (1927).
[81] This experiment has been repeated by Lachman with the following result: Using benzil instead of diphenylglycol aldehyde, and heating for only six hours but otherwise duplicating Danilov's experimental details, all of the benzil was converted into benzilic acid.



In this formula R may be an aryl or alkyl radical or hydrogen. When such a compound is treated with mercuric oxide, or with an alcoholic solution of silver nitrate, hydrogen iodide is removed and the aryl group migrates to the position vacated by the iodine atom.

Tiffeneau, who discovered this reaction in connection with the compound $C_6H_5—CHOH—CH_2I$, assumed that the hydrogen and iodine are removed from the same carbon atom.[82] This type of elimination he called unilateral. The removal of an atom or group from one carbon with an atom from an adjacent carbon is referred to as bilateral elimination.

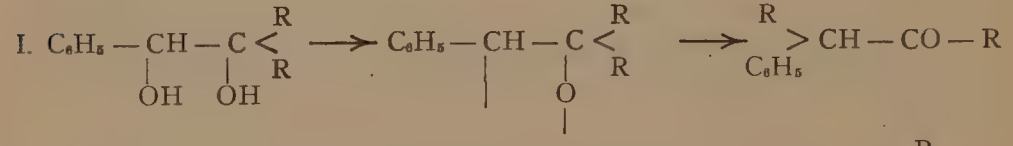
$$C_6H_5—CHOH—CH_2I \longrightarrow C_6H_5—CHOH—CH< + HI$$
$$C_6H_5—CHOH—CH< \longrightarrow CHOH=CH—C_6H_5$$
$$CHOH=CH—C_6H_5 \longrightarrow C_6H_5—CH_2—CHO$$

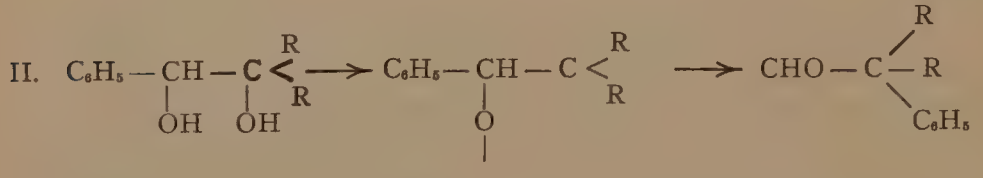
This mechanism is supported by the behavior of compounds having the structure $C_6H_5—CROR—CRHI$ which, under similar treatment, yield $C_6H_5—CR=CROR$. The substitution of an alkyl radical for the hydroxyl hydrogen prevents the last step in the process outlined above and the unsaturated intermediate becomes the final product.

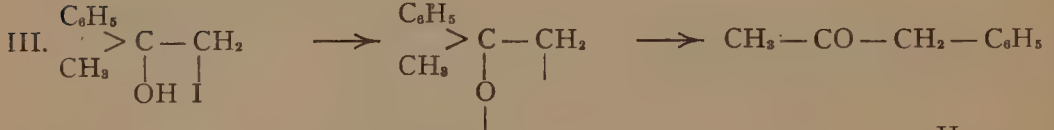
Mercuric oxide and silver salts are specific reagents for this reaction. When an iodohydrol is warmed with alcoholic potassium hydroxide, bilateral elimination of hydrogen halide occurs if this is structurally possible. In this case, an ethylene derivative is formed and no rearrangement is accomplished. If there is no replaceable hydrogen on the carbon atom adjacent to the one holding the halogen, then alcoholic potash merely replaces the halogen with the hydroxyl group. Michael concludes, therefore, that the rearrangement proceeds through the formation of a silver or mercury derivative of the hydrol.[83] Miss Lévy [84] made an attempt to place the glycol and the iodohydrol reactions in the same category by

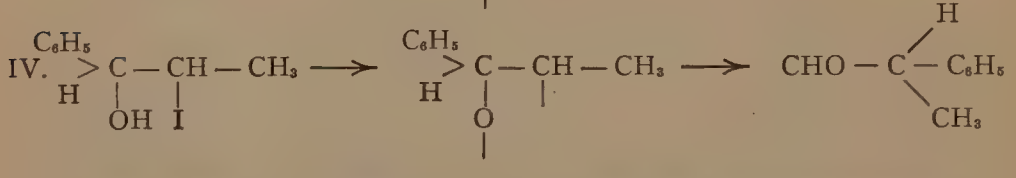
[82] Tiffeneau, *Bull. soc. chim.* (4), **1**, 1205 (1907); Hoering, *Ber.*, **41**, 3081 (1908).
[83] Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920).
[84] Lévy, *Bull. soc. chim.* (4), **33**, 1655 (1923).

assuming that in the former water is eliminated between the two hydroxyl groups, and in the latter hydrogen iodide is formed by removal of the hydroxyl hydrogen with the iodine. The glycol reacts according to equation I or II and the iodohydrol follows III or IV.

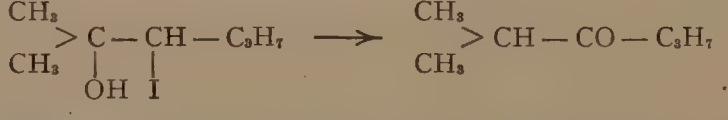








The analogy between the glycols and the iodohydrols fails in some instances. Thus 2-methyl-3-iodo-hexanol-2 is converted by silver nitrate into 2-methyl-hexanone-3.



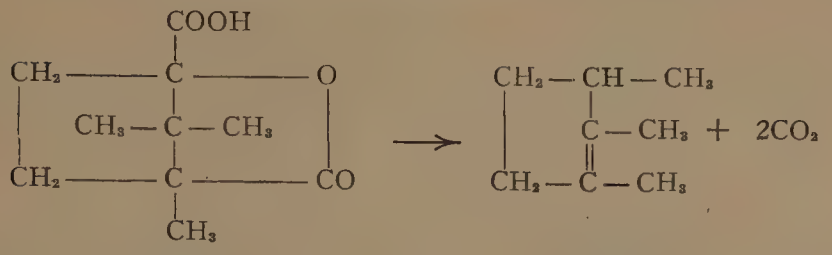
Here apparently the hydroxyl group, instead of a carbon radical, has shifted. There is the further possibility that water is first eliminated with the establishment of a double bond between the α and β carbon atoms and that hydrolysis of the iodine is the second step. The resulting enol would yield the product which was actually isolated.

TERPENES

In the preparation of laurolene from camphanic acid by distillation, a *gem* * methyl group shifts to an adjacent carbon atom.[85]

* See footnote 93.

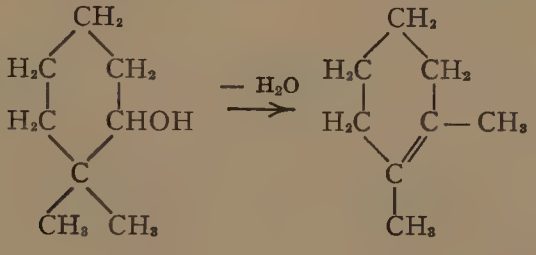
[85] Noyes, *J. Am. Chem. Soc.*, **32**, 1068 (1910).



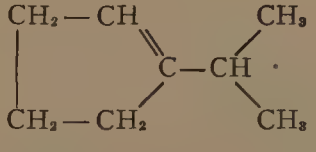
Camphanic acid *Laurolene*

Laurolene is also one of the products formed from amino-camphanic acid by treatment with nitrous acid.[86] This, likewise, involves the migration of a methyl group.

Similarly the dehydration of 2,2-dimethylcylcohexanol-1 results in the transfer of a *gem* methyl group to an ortho position.[87]



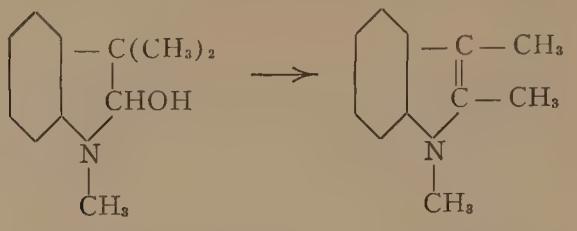
A smaller part of the cyclohexanol rearranges in a different way, yielding a five-membered ring to which Meerwein assigned the formula



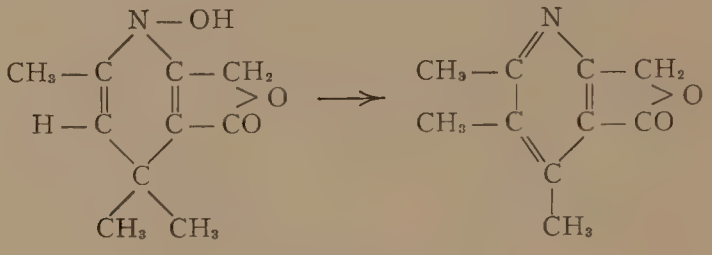
The conversion of isogeraniolene into a derivative of hemellitic acid is another example of this type.[88]

In many derivatives of indol the shift of an alkyl radical is brought about by heat alone. Any salt of the tertiary base, 1-methyl-3-3-dimethylindolinol-2, when heated on a water bath, loses water yielding 1,2,3-trimethylindol.[89]

[86] Noyes and L. R. Littleton, *J. Am. Chem. Soc.*, **35**, 75 (1912).
[87] Meerwein, *Ann.*, **417**, 255 (1918).
[88] Baeyer, *Ber.*, **32**, 2429 (1899).
[89] Brunner, *Monatsh.*, **17**, 253 (1896); **21**, 156 (1900); Knorr, *Ber.*, **36**, 1272 (1903).

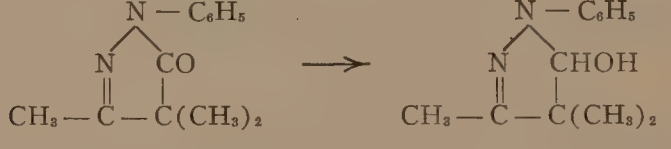


Similar results have been obtained in connection with some of the terpenes [90] and with several hydrated pyridine derivatives.[91] One of the many examples cited by Wolff is the following:

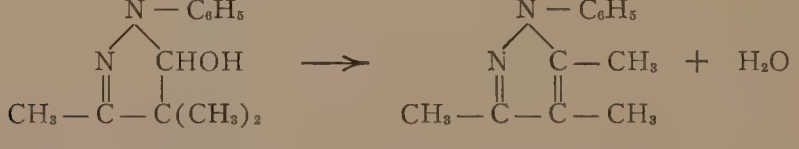


PYRAZOLONES

Transpositions in the pyrazol series have been reported by Knorr and by Jochheim.[92] The ketone, 1-phenyl-3,4,4-trimethyl-pyrazolon is reduced by sodium amalgam to 1-phenyl-3,4,4-trimethyl-5-oxypyrazoline.



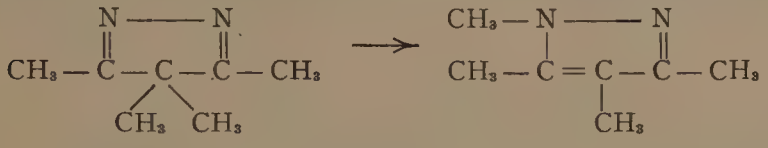
The latter, when warmed with a mineral acid, is converted into 1-phenyl-3,4,5-trimethylpyrazol.



A case in which a radical of the "*gem*-dimethyl" [93] group migrates to nitrogen and without change in the state of saturation in

[90] Wallach, *Ann.*, **279**, 366 (1894); **286**, 90 (1895); Tiemann, *Ber.*, **30**, 321 (1897).
[91] Wolff and Conroy, *Ann.*, **322**, 351 (1902).
[92] Knorr, *Ber.*, **36**, 1272 (1903); Jochheim, "Dissertation," Jena, **1896**.
[93] The term *gem-dimethyl* was proposed by A. von Baeyer to designate two methyl groups attached to the same carbon atom, *Ber.*, **31**, 2098 (1898).

the molecules is found in 3,4,4,5-tetramethylpyrazolenin.* When warmed with methyliodide it yields 1,3,4,5-tetramethylpyrazol.



This reaction, presumably, involves the addition and subsequent elimination of methyl iodide. The O-alkyl-hydroxyquinolines are converted into N-alkyl-quinolones in the same way.[94]

* For nomenclature see Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Vol. 2:3, p. 364 (1920).

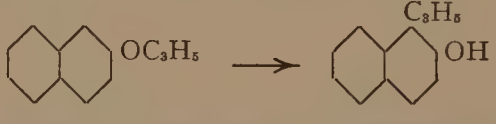
[94] Knorr, *Ber.*, **30**, 929 (1897).

Chapter IV

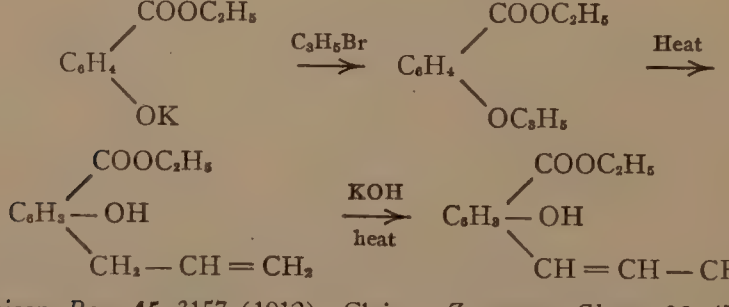
Migrations from Oxygen to Carbon

PHENYL-ALLYL ETHERS AND RELATED COMPOUNDS

When the potassium salt of β-naphthol is warmed with allyl bromide in acetone an oil is formed. Before it is subjected to distillation the oil is colorless and is characterized by a pleasant odor, insolubility in basic solutions and failure to produce a color with ferric chloride. When distilled under 12 mm. pressure the boiling point gradually rises and the last fraction crystallizes on cooling. The new product is isomeric with the oil. It is soluble in alkali and forms a bluish-green compound with ferric chloride. The change is irreversible and when the oil is heated in a sealed tube to 210° C. the conversion is quantitative.[1] It is represented by the equation



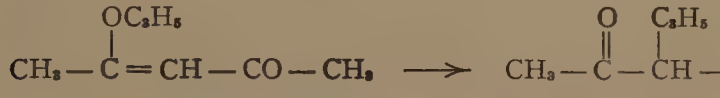
Guaiacol allyl ether is changed quantitatively into *iso*-eugenol when heated to 230° C. In a similar way O-allyl salicylic acid is isomerized and the resulting C-allyl salicylic acid can be further changed to propenyl salicylic acid by treatment with hot concentrated alkali. The last change is a shift in the position of the double bond. The reactions, beginning with the potassium derivative of the ethyl ester, are indicated below:



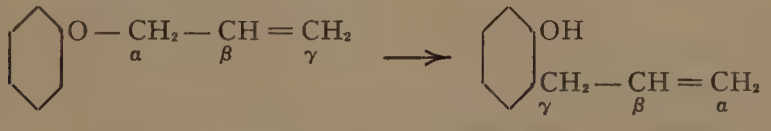
[1] Claisen, *Ber.*, **45**, 3157 (1912); Claisen, *Z. angew. Chem.*, **36**, 478 (1923). (1923).

Allyl ether derivatives of other phenols change in the same manner.[2] The reaction is not limited to the aromatic series.[3] The O-allyl derivative of acetoacetic ester is converted by heat treatment into the isomeric form.

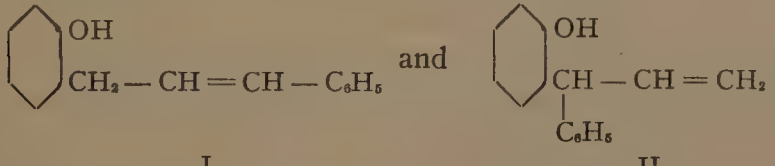
Under similar conditions O-allyl acetylacetone is changed to the C-derivative.



Claisen and Tietze believe that the allyl radical does not attach itself to a cyclic nucleus through the same carbon atom that was bound to oxygen.[4] They represent the conversion of phenyl allyl ether to allyl phenol as follows:

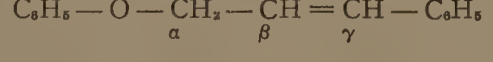


In the case of allyl ethers the result is the same whether the new attachment is made through the α-carbon or the γ-carbon atom. Substituting the cinnamyl radical for the allyl group they succeeded in isolating two isomeric cinnamyl phenols.



I II

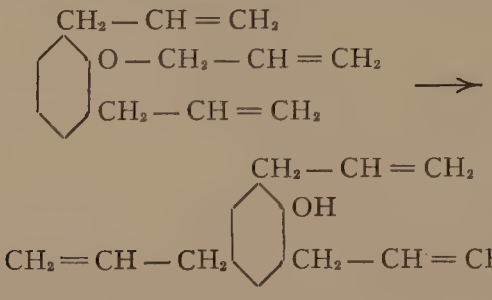
They assume that I is formed by direct substitution when sodium phenolate is heated with cinnamyl bromide whereas II is obtained, by rearrangement, from the ether,



through an attachment of the γ-carbon atom to the ring. The simultaneous release of the cinnamyl radical from oxygen would compel a shift in the position of the double bond.

[2] Claisen, *Ann.*, **418**, 69 (1919).
[3] v. Braun and Schirmacher, *Ber.*, **56**, 538 (1923).
[4] Claisen and Tietze, *Ber.*, **58**, 275 (1925); *ibid.*, **59**, 2344 (1926).

It is possible to introduce three allyl groups into the same phenol nucleus through the Claisen rearrangement. The two positions ortho to the hydroxyl are first occupied but when allyl-2,6-diallylphenyl ether is heated, symmetrical triallyl phenol is produced.

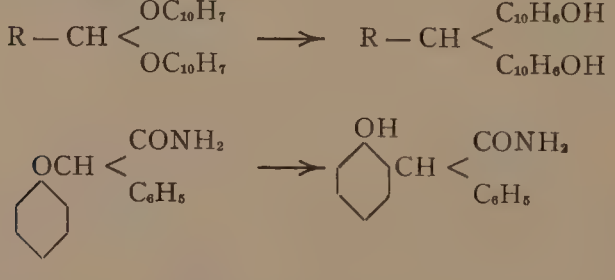


The fact that substitution can occur in the para position throws doubt upon the theory of attachment through the γ-carbon atom.

The methyl group in methoxybenzene fails to migrate from oxygen to the ring. The substitution of one, two or three phenyl radicals for hydrogen in the methoxy group enhances its mobility. Thus phenylbenzyl ether is partly converted into 4-hydroxydiphenylmethane by the catalytical influence of zinc chloride at 160° C.[5]

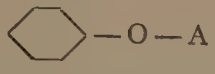
Diphenylmethyl groups and triphenylmethyl groups also have been introduced into the phenol ring by this process.

Other types of substitution also make possible the conversion of a phenyl ether into an alkylated phenol. Of the following examples, the first was observed by Claisen[6] and the second by Bucherer and Grolée.[7]

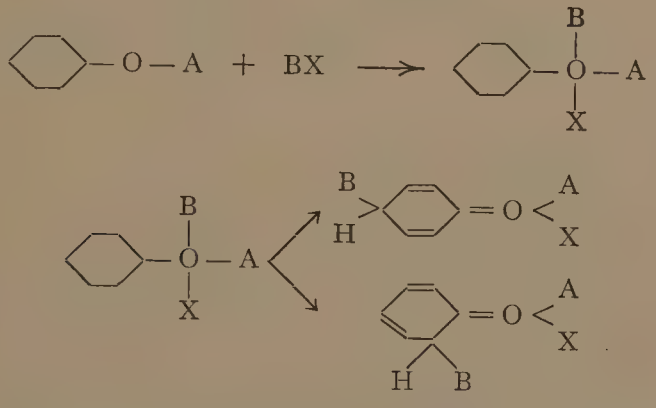


[5] Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927).
[6] Claisen, *Ann.*, **237**, 261 (1887).
[7] Bucherer and Grolée, *Ber.*, **39**, 986 (1906).

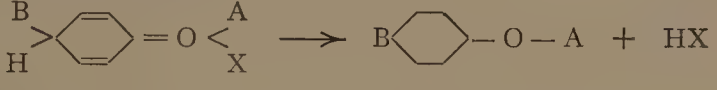
Van Alphen assumes that all reactions involving substitution in the nucleus of a phenol or a phenyl ether begin with addition to the oxygen. The oxonium compound then undergoes rearrangement. Writing



for any phenol derivative and BX for a compound that reacts with it, the course of the substitution process is outlined as follows:



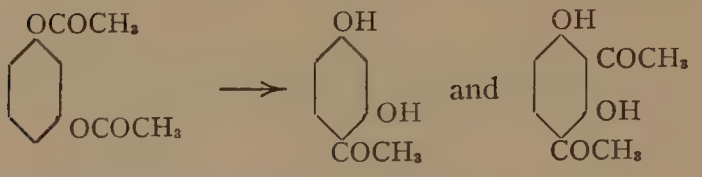
The last step is represented by loss of HX and the return of the ring to the benzoid form.



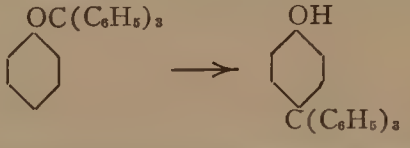
The analogy of this reaction with substitution in aromatic amines and the fact that some colored addition products have been isolated are the principal evidences presented in support of this mechanism. It is an extension of an earlier theory which was supported by Blanksma [8] and criticized by Vorländer.[9]

In the chlorination of acetanilide,[10] chlorine replaces hydrogen in the amino group, then migrates to the ring; and in the production of resacetophenone, acetyl chloride acts upon resorcinol to form a diacetate which can be isolated and which changes to a mixture of resacetophenone and resodiacetophenone when warmed with zinc chloride.[11]

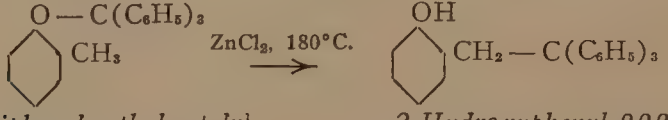
[8] Blanksma, *Rec. trav. chim.*, **23**, 2002 (1904).
[9] Vorländer, *Ber.*, **58**, 1893 (1925).
[10] Blanksma, *Rec. trav. chim.*, **21**, 366 (1902).
[11] Eijkman, *Chem. Zentr.*, **1904**, I, 1597; **1905**, I, 814; Heller, *Ber.*, **45**, 418 (1912).



Triphenylmethyl-phenyl ether, prepared by treating an ether solution of potassium phenolate with triphenylmethyl chloride, is a crystalline body melting at 103° C. By treatment with warm zinc chloride, it is changed to *para*-hydroxytetraphenylmethane.[12]



A shift to an *ortho* side chain is reported also by Van Alphen.



Triphenylmethyl-o-tolyl ether, m.p. 113°C.

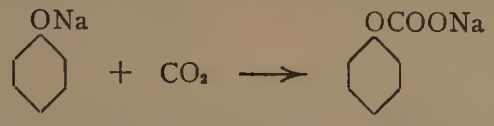
α-2-Hydroxyphenyl-βββ-triphenylethane, m.p. 185°C.

KOLBE'S SYNTHESIS

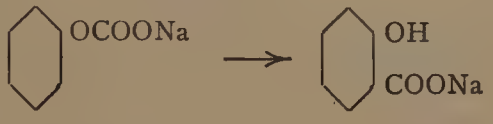
Kolbe heated sodium phenolate to 180° C.-220° C. in a current of carbon dioxide. Half of the phenol distilled over in the free state and half was converted into the disodium derivative of salicylic acid.[13]

A modification of Kolbe's method, developed by Schmitt, permits the total conversion of phenol into salicylic acid.[14] In this process dry sodium phenolate is saturated with carbon dioxide at the temperature of the laboratory. The theoretical quantity of gas is absorbed in the formation of sodium phenyl carbonate. When heated to 120° C.-140° C. in an autoclave this yields sodium salicylate. This result led to the assumption that sodium phenyl carbonate is an intermediate in the production of salicylic acid from phenol.

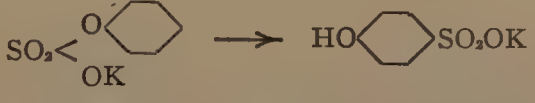
[12] Van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).
[13] Kolbe, *Ann.*, **113**, 126 (1860); Kolbe and Lautemann, *Ann.*, **115**, 203 (1860); Kolbe, *J. prakt. Chem.* (2), **8**, 41, 336 (1874); (2), **11**, 24 (1875).
[14] Schmitt, *J. prakt. Chem.* (2), **31**, 397 (1885).



The last phase of the process has been regarded as a rearrangement as indicated by the equation

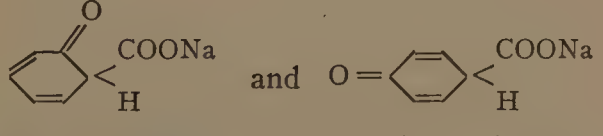


This view was supported by the fact that potassium phenylsulfate is converted by heat into a salt of *para*-hydroxybenzenesulfonic acid.[15]



An objection to the above mechanism was made by Tijmstra, who found that sodium phenyl carbonate dissociates at low temperatures, the dissociation pressure of carbon dioxide being more than one atmosphere at 85° C.[16] This is below the temperature required to produce salicylic acid. He admits that the sodium phenyl carbonate may be an intermediate in Schmitt's process where the reaction is carried out at 110° C.-140° C. in a sealed tube or in an autoclave, but maintains that a different mechanism must be applied when the reaction occurs in an open vessel. He believes Kolbe's intermediate to be $C_6H_4(ONa)COOH$. This is probably the correct interpretation of the reaction and if so Kolbe's synthesis does not represent a rearrangement at all. It is simply a direct absorption of carbon dioxide in a position *ortho* (or at higher temperatures, *para*) to the ONa group.

Brunner regards the intermediate as an addition of carbon dioxide to a quinoid form of the phenol.[17] The structures proposed are



The final stage, according to Brunner, is the isomeric change of the quinoid to the benzoid form.

[15] Baumann, *Ber.*, **11**, 1910 (1878). See also the work of J. Moll Van Charante, *Rec. trav. chim.*, **27**, 59 (1908).
[16] Tijmstra, *Ber.*, **38**, 1374 (1905).
[17] Brunner, *Ann.*, **351**, 326 (1907).

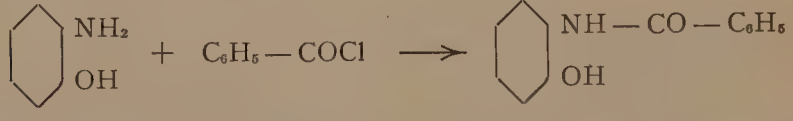
Chapter V

Migrations Between Oxygen, Nitrogen, and Sulfur

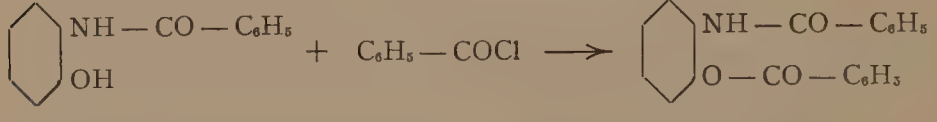
MIGRATIONS FROM OXYGEN TO NITROGEN

ACYLATED AMINOPHENOLS

An *ortho*-aminophenol in pyridine or in aqueous alkaline solution is acylated by treatment with an acid chloride. The N-ester is the first product formed.



With an excess of the reagent the hydroxyl group is attacked and a diacyl derivative is obtained.



The diacyl derivative can be half hydrolyzed by treatment with one equivalent of alkali. In this way, one of the acyl groups can be removed without the other and when this is done, the radical which has resisted hydrolysis is found linked to nitrogen. On complete saponification the original aminophenol is regenerated.

If monoacetyl-*ortho*-aminophenol is first prepared and the benzoyl group is introduced later, the resulting diacyl derivative, when half hydrolyzed, yields a product in which the benzoyl group is attached to nitrogen. If the two acyl radicals are introduced into the aminophenol in the reverse order, the same hydrolysis product is obtained. Similar results have been observed in connection with other pairs of acyl radicals.[1] Auwers concluded that the amino nitrogen always acquires the acyl group if only one is introduced into an *ortho*-aminophenol and either directly or by rearrangement

[1] Böttcher, *Ber.*, **16**, 629 (1883).

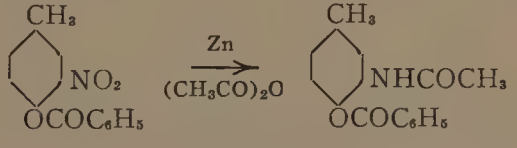
acquires the heavier radical if two acyl groups are present.[2] Many exceptions to this rule have been found as will be shown later.

Rearrangement may occur during the process of acylation or during the subsequent hydrolysis. In the first case, isomeric diacyl derivatives are not obtained. The same compound is formed regardless of the order in which the acyl groups are introduced. If rearrangement does not occur during acylation, a pair of isomeric esters can be obtained by introducing the two acyl radicals in different orders, but the two isomers, when half hydrolyzed, yield the same monoacyl derivative.

By indirect methods, the monoacyl O-esters of *ortho*-aminophenols have been made but as a rule they change spontaneously into the corresponding N-derivatives so that the latter are the products usually obtained in the ordinary processes of acylation. This does not apply to *meta* and *para* aminophenols.[3] The *peri*-position in an amino naphthol is within the range of this reaction. The benzoylation of 8-acetylamino-1-hydroxy-naphthalene results in the formation of 8-benzoylamino-1-acetyl-oxynaphthalene.[4]

It is possible to isolate two isomeric acetyl-benzoyl-derivatives of *ortho*aminoparacresol. One is obtained by the action of acetyl chloride on the mono-benzoyl derivative of the aminophenol.

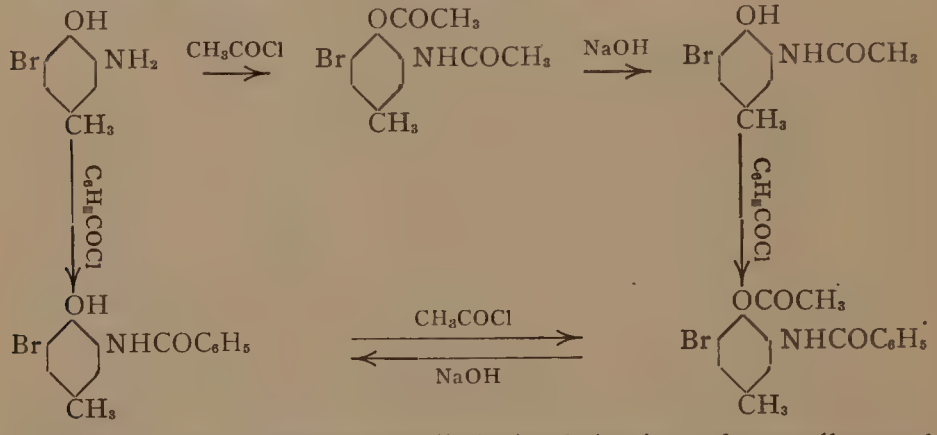
The second is made by reducing the benzoyl derivative of *ortho*-nitroparacresol with zinc in the presence of acetic anhydride.[5]



Each of these diacyl derivatives, when half hydrolyzed, yields the same monoacyl derivative—the N-benzoyl ester. Raiford converted the base 2-amino-4-methyl-6-bromophenol into a diacetate by treat-

[2] Auwers, *Ber.*, **37**, 2249, 3903 (1904).
[3] Raiford and Couture, *J. Am. Chem. Soc.*, **44**, 1792 (1922); Raiford and Iddles, *ibid.*, **45**, 469 (1923).
[4] Raiford and Clark, *Detroit Meeting Am. Chem. Soc.* (1927).
[5] Einhorn and Pfyl, *Ann.*, **311**, 34 (1900); Auwers and F. Eisenlohr, *Ann.*, **369**, 209 (1909).

ment with acetic anhydride and sodium acetate. He hydrolyzed the product with cold dilute sodium hydroxide and obtained a mono-acetyl derivative in which the acetyl group was attached to nitrogen. The benzoyl group was then introduced by the Schotten-Baumann method and the new diacyl derivative was half hydrolyzed. The resulting ester was identified as 2-benzoylamino-4-methyl-6-bromphenol.[6] The results of his investigations with this base are summarized in the diagram below.



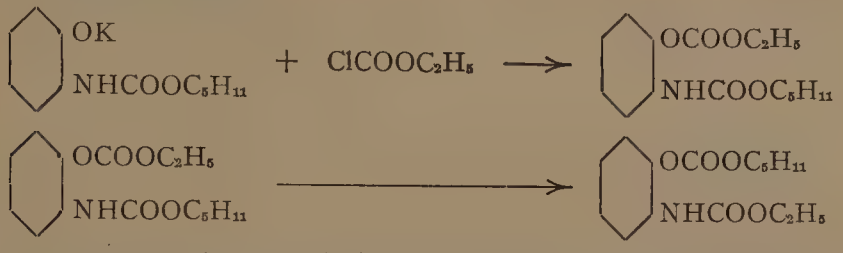
Auwers and Eisenlohr studied the behavior of acetylbenzoyl derivatives of 2-amino-4-methylphenol. When the N-acetyl derivative of this phenol was treated with benzoyl chloride and alkali, the same diacyl derivative was obtained as that formed when 2-nitro-4-methylphenyl benzoate was reduced by zinc dust and acetic acid in the presence of acetic anhydride. It was regarded as the O-benzoyl-N-acetyl compound. When hydrolyzed by alkali, it gave only the N-benzoyl derivative. They reached the conclusion that the difference in the weights of the two radicals determines the tendency to migrate.[7]

Raiford and Couture found that generally the heavier group attaches to nitrogen, but they also found exceptions to this rule.[8]

Ransome reports many reactions in which the lighter of the two groups in a substituted *ortho*-aminophenol is the one retained by the amino nitrogen.[9] In fact, this is said to be an invariable rule when applied to the carboxylester groups, COOR and $COOR_1$. In alkaline solution, chlorocarbonic-ethylether reacts with hydroxy-

[6] Raiford, *J. Am. Chem. Soc.*, **41**, 2068 (1919).
[7] Auwers and Eisenlohr, *Ann.*, **369**, 209 (1909).
[8] Raiford and Couture, *J. Am. Chem. Soc.*, **44**, 1792 (1922); **46**, 2305 (1924).
[9] Ransom, *Am. Chem. J.*, **23**, 1 (1900).

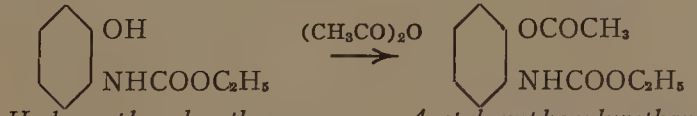
phenylisoamylcarbamate yielding the carbamyl derivative of *ortho*-hydroxyphenylurethane.



Numerous examples of this kind led Ransom and Nelson to conclude that "when two carboxyl radicals (COOR and $COOR_1$) are introduced into the molecule of an *ortho*-aminophenol, the lighter one becomes attached to nitrogen, the position not being influenced by the order in which the groups are introduced; and that to accomplish this, a molecular rearrangement occurs in one case." This is often true also when both of the radicals are carbonyls (COR and COR_1). "In case one radical is carbonyl and the other carboxyl the latter becomes attached to nitrogen without being influenced by the relative weights of the entering groups." [10] The result, however, is never quantitative.

Partial rearrangement occurs in the diacyl regardless of the order in which the groups are introduced.[11] The same thing occurs with structurally isomeric groups such as *normal* and *iso* carbopropoxy groups. An exception was found [12] in the case of the group $C_4H_9CO_2$. The *n*-butyl carbonate of *iso*-butyl-*ortho*-hydroxycarbanilate, $C_4H_9CO_2OC_6H_4NHCO_2C_4H_9$ (*n* and *iso*), rearranges, partially, yielding a mixture of the isomeric forms whereas the *iso*-butyl carbonate of *n*-butyl-*ortho*-hydroxycarbanilate, $C_4H_9CO_2OC_6H_4NHCO_2C_4H_9$ (*iso* and *n*) shows no tendency to change.

Acetyloxyphenylurethane is obtained through the action of acetic anhydride and an alkali upon hydroxyphenylurethane.



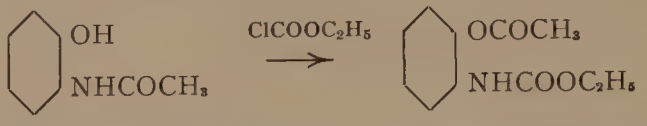
Hydroxyphenylurethane *Acetyloxyphenylurethane*

[10] Ransom and Nelson, *J. Am. Chem. Soc.*, **36**, 390 (1914); Ransom and Nelson, *Proc. Indiana Acad. Sci.*, **1913**, 145. Rate measurements on rearrangements of this type were made by Stieglitz and Upson, *Am. Chem. J.*, **31**, 458 (1904).

[11] Nelson and Davis, *J. Am. Chem. Soc.*, **48**, 1677 (1926).

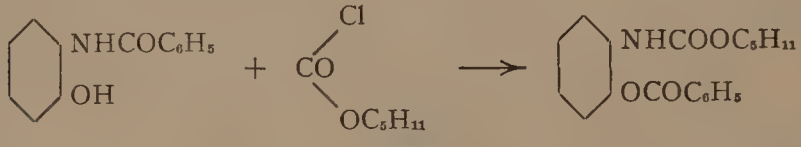
[12] Nelson and Aitkenhead, *J. Am. Chem. Soc.*, **48**, 1680 (1926).

The same product is formed when N-acetyl-*ortho*-aminophenol is treated with ethylchloroformate.



Hydroxyphenyl*iso*amylurethane and benzoyl chloride yield benzoyloxyphenyl*iso*amylurethane.

Benzoyl-*o*-aminophenol, when mixed in alkaline solution with *iso*amylchloroformate, is converted into the same product. In the latter case the benzoyl group evidently leaves the nitrogen and attaches to the oxygen atom.

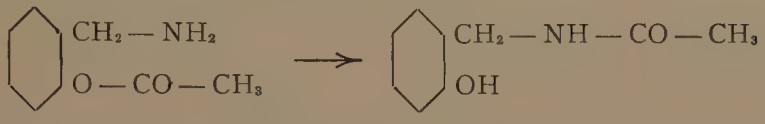


Raiford and Lankelma investigated the influence of the relative acidities of the migrating radicals. Radicals from acids of known ionization constants were used in pairs. They were introduced into 2-amino-4-methyl-6-chlorophenol. It was found that in most cases the same diacyl derivative was formed regardless of the order of introduction, so that rearrangement occurred during acylation. The more acidic group was attached to the nitrogen atom. In a few instances isomeric diacyl derivatives could be prepared but with most of these pairs the more acidic group was found on nitrogen after partial hydrolysis. In these cases rearrangement occurred during hydrolysis. In one case the less acidic member of the pair was retained by nitrogen. The acyls that gave anomalous results were the benzoyl and 3,5-dinitrobenzoyl groups. "The same diacyl derivative was obtained by introduction of the radicals in different orders, and hydrolysis of the product gave only 2-benzoylamino-4-methyl-6-chlorophenol and 3,5-dinitrobenzoic acid." [13] Rearrangement occurred during acylation and in this instance the lighter and the less acidic group appeared on the nitrogen atom. A similar result with the acetyl and *para*-nitro-

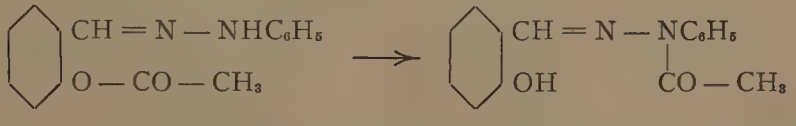
[13] Raiford and Lankelma, *J. Am. Chem. Soc.*, **47**, 1111 (1925).

benzoyl groups had been observed at an earlier date by Raiford and Couture.

The acyl group wanders from phenol oxygen to nitrogen in the α-position in an *ortho*-side-chain. The O-acetyl derivative of *ortho*-hydroxybenzylamine is unstable.



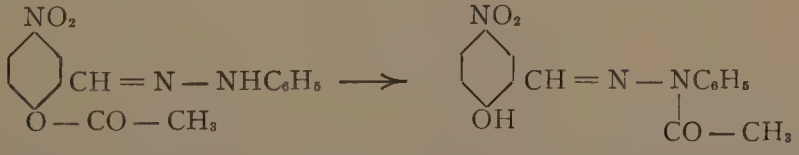
Nor is the reaction limited to the α-position. It may extend to the β and γ-positions. In such cases, however, the application of heat or the use of a catalyst is generally necessary to bring about the rearrangement. Both forms are stable enough to permit isolation. Thus the phenylhydrazone of the acetyl derivative of salicylaldehyde can be prepared but upon heating the hydrazone with glacial acetic acid the rearrangement occurs.



As a typical method of isolating the isomeric forms, the work of Auwers on a nitro-derivative of salicylaldehyde phenylhydrazone may be of interest:

Slowly, and with efficient cooling, 5 grams of freshly distilled acetyl chloride was added to a solution of 5 grams of *m*-nitrosalicylaldehyde-phenylhydrazone in 50 grams of pyridine. The mixture was allowed to stand over night and the ester was then precipitated by adding an excess of very dilute sulfuric acid. The product was dried on a water bath and recrystallized from alcohol or chloroform. Red crystals melting at 191°C. were obtained.

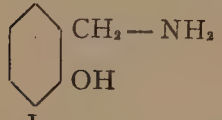
A glacial acetic acid solution of the red crystals was warmed on a water bath for five hours. On cooling a crystalline mass, containing both isomeric forms, was obtained. The N-ester was extracted from the mixture with dilute sodium hydroxide and reprecipitated from the alkaline solution with hydrochloric acid. The product when crystallized from ethyl acetate consisted of white needles melting at 165°C. The structure of the compound was proved by synthesizing it from nitrosalicylaldehyde and α-acetylphenylhydrazine.[14]



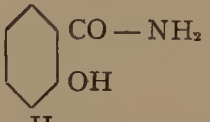
[14] Auwers and Bürger, *Ber.*, **37**, 3929 (1904). See also Auwers and Bondy, *Ber.*, **37**, 3905, 3915 (1904).

Auwers prepared O-acetyl derivatives of the phenylhydrazones of many derivatives of salicylaldehyde. They were stable enough to be isolated, but were easily isomerized by warming with acetic acid or with pyridine. No rearrangement could be obtained with similar compounds having the hydroxyl and aldehyde groups in *meta* or *para* position.

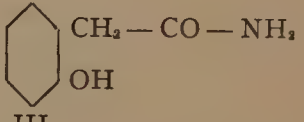
The acidity and mobility of the acyl radical and the basicity of the amino or imino group to which it migrates are important factors in the rearrangement. An acetyl group shifts more readily than does the benzoyl radical. With a series of nitrogen bases of varying strengths, it is possible to find limiting cases where the rearrangement occurs with the more mobile acetyl group and fails with the benzoyl derivative. In the following series of bases, the O-acetyl derivatives change to N-esters with increasing difficulty from I to III and the O-benzoyl derivative of III does not undergo the rearrangement.



I

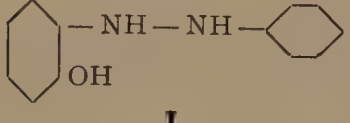


II



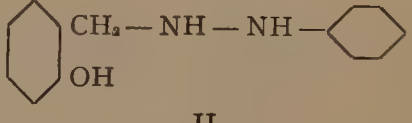
III

Another example is found in the structures:



I

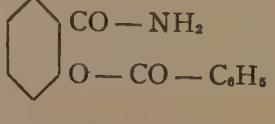
and



II

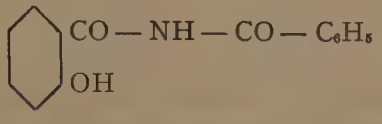
An O-ester of the hydrazo-compound, I, is quite stable. It changes in the presence of acetic acid or of alcoholic hydrogen chloride. But an O-ester of the phenylhydrazine derivative, II, goes over spontaneously to the isomeric form.

There is some uncertainty concerning the structures of the benzoyl derivatives of salicylamide. All agree that the labile ester which melts at 144° C. has the structure:

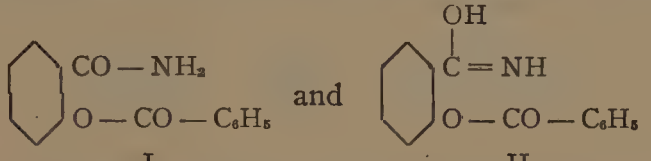


When heated above its melting point it is converted into an isomeric ester which melts at 208° C. This more stable derivative

was first prepared by Gerhardt and Chiozza [15] by heating a mixture of benzoyl chloride and salicylamide. It has generally been regarded as the N-ester.[16] On the other hand, Titherley and Hicks [17] have questioned the validity of arguments in favor of this structure.

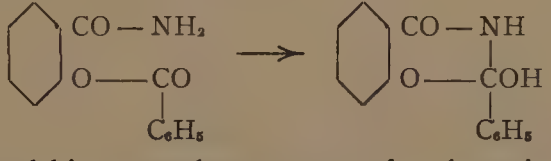


They considered it more likely that both of these compounds are O-esters and they wrote the formulas as follows:

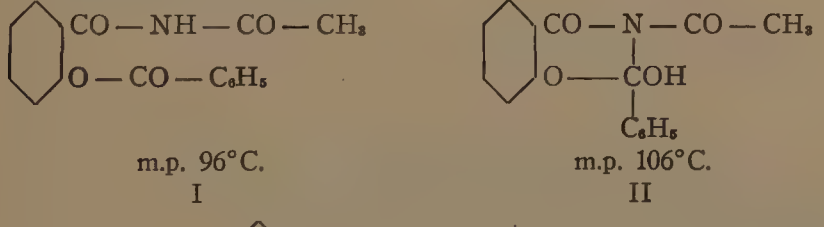


I and II

Later, McConnan and Titherley [18] discredited formula II and presented evidence that the changes comprise the formation of a cyclic derivative.



Titherley and his co-workers account for the existence of three acetyl derivatives of benzoylsalicylamide by assuming that one of them has the cyclic structure.



m.p. 96°C. I

m.p. 106°C. II

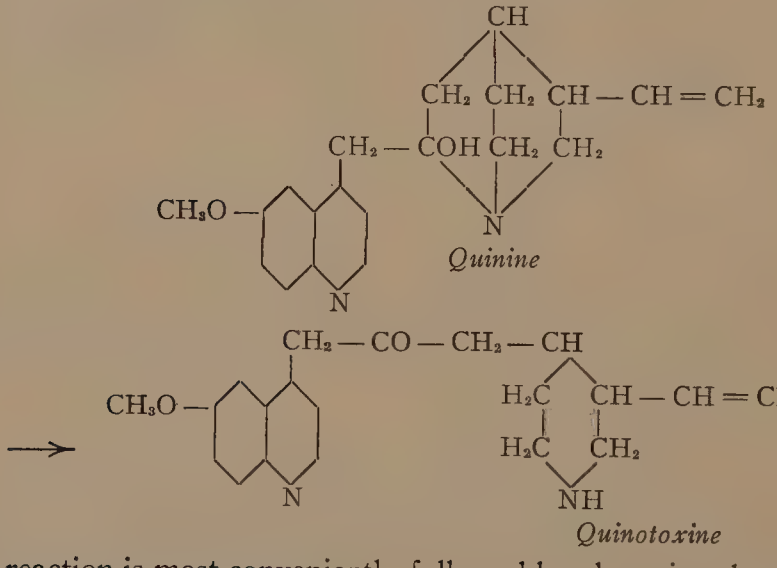
m.p. 124°C. III

[15] Gerhardt and Chiozza, *Ann. Chim. Phys.*, **46**, 129 (1856).
[16] Auwers, *Ber.*, **38**, 3256 (1905); **40**, 3507 (1907); Einhorn and Schupp, *Ber.*, **38**, 2793 (1905); Einhorn and Haas, *Ber.*, **38**, 3627 (1905); McConnan, *J. Chem. Soc.*, **91**, 198 (1907).
[17] Titherley and Hicks, *J. Chem. Soc.*, **87**, 1207 (1905).
[18] McConnan and Titherley, *J. Chem. Soc.*, **89**, 1318 (1906).

One of these (said to be I) is formed by boiling Gerhardt's benzoylsalicylamide (p. 127) with acetic acid. The second is formed from the same compound by treatment with acetyl chloride and pyridine at room temperature, and the third is obtained by acetylating with acetyl chloride and acetic anhydride at —15° C.

CINCHONA ALKALOIDS

Several closely related nitrogen bases occur in the bark of the cinchona trees. Among the more important of these are quinine and cinchonine. Each of these alkaloids is isomerized by treatment with an aqueous solution of a weak acid such as citric acid or acetic acid. The reaction is inhibited by a high concentration of hydrogen ions.[19] The change consists in the migration of hydrogen from a hydroxyl group to nitrogen in the quinoline residue of the molecule as indicated by the following structures:



The reaction is most conveniently followed by observing the change in the optical activity of the solution. One of the asymmetric carbon atoms is involved in the rearrangement.[20]

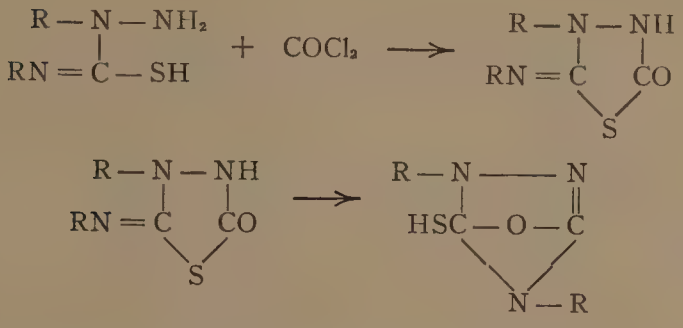
THIOBIAZOLONES

Phosgene reacts with α-thiosemicarbazides yielding labile thiobiazolones which isomerize when heated to triazolone derivatives.[21]

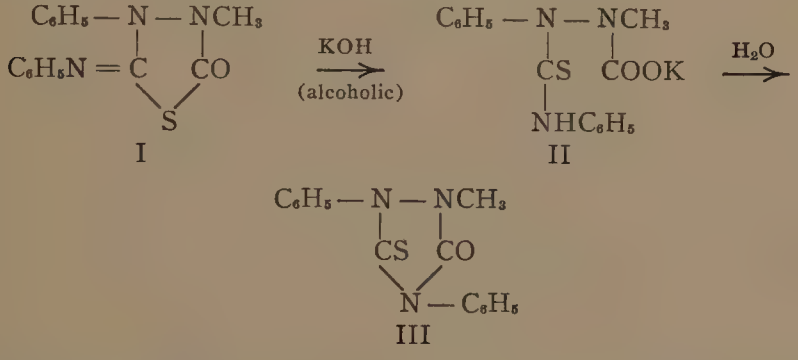
[19] Biddle, *J. Am. Chem. Soc.*, **38**, 901 (1916).

[20] For a discussion on the stereoisomerism of the cinchona alkaloids see Adolf Kaufmann and Max Huber, *Ber.*, **46**, 2913 (1913); P. Rabe, *Ann.*, **373**, 85 (1910); *Ber.*, **44**, 2088 (1911).

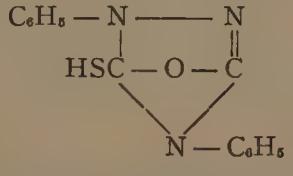
[21] Busch and Limpach, *Ber.*, **44**, 560 (1911).



The mechanism of the transformation as applied to 1-phenyl-2-methylthiobiazolon-5-anil is, probably, as follows:



In this case formula III represents the final product but when hydrogen occupies the place of the methyl group an additional shift occurs and a compound of the following structure is formed.



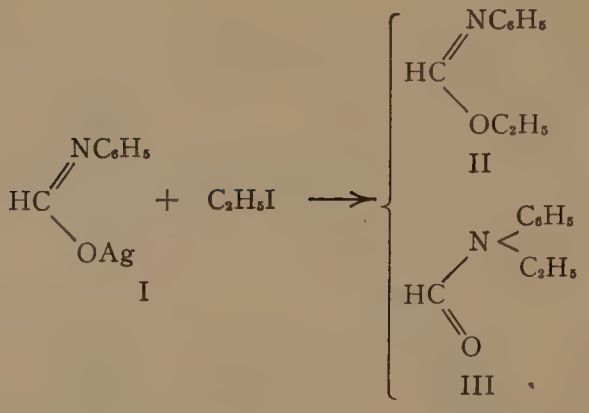
MIGRATIONS FROM OXYGEN TO NITROGEN

IMIDOESTERS

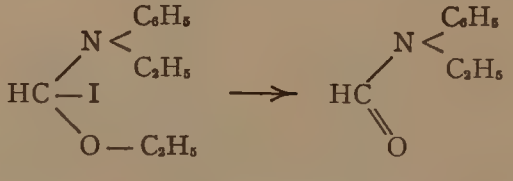
An imidoester may be prepared from the silver salts of an amide by heating the latter for several hours in ether with an alkyl iodide.[22] Wheeler and Johnson found that when silver formanilide, I, was heated with ethyl iodide in an open vessel ethylphenylimidoformate, II, was produced but when the same reagents were heated to 100° in a sealed tube an isomeric product, N-ethylformanilide, III, was obtained.[23]

[22] Tafel and Enoch, *Ber.*, **23**, 103, 1550 (1890); Comstock, *Ber.*, **23**, 2274 (1890).

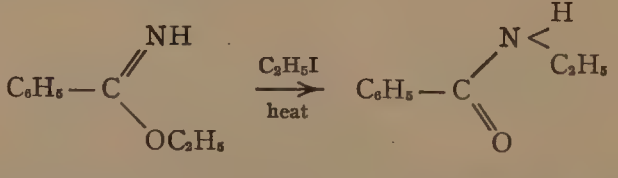
[23] Wheeler and Johnson, *Am. Chem. J.*, **21**, 185 (1899).



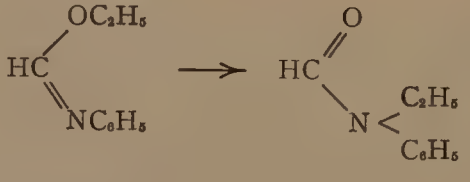
It is possible that compound II is an intermediate when the reaction is carried out at the higher temperature. Compound III would then be formed by the migration of the ethyl group from oxygen to nitrogen. The authors suggested a different mechanism, viz., the reaction of compound II with a second molecule of ethyl iodide by direct addition and subsequent elimination of ethyl iodide involving the removal of the ethyl group attached to oxygen.



Benzoimidoethylester, when heated to 100° C. with ethyl iodide and ether, yields ethylbenzamide.



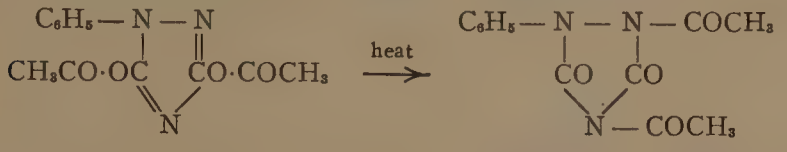
The ethyl ester of formanilide is changed by heat alone to ethylphenylformamide.[24]



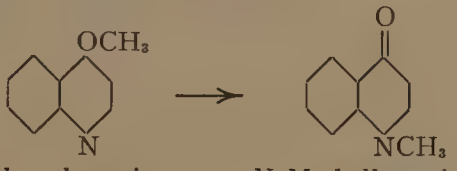
[24] Wislicenus and Korber, *Ber.*, **35**, 164 (1902).

TRIAZOLES

In some triazole derivatives similar migrations occur.



The transference of a radical from oxygen to nitrogen occurs also when methoxykynurine is heated.[25]



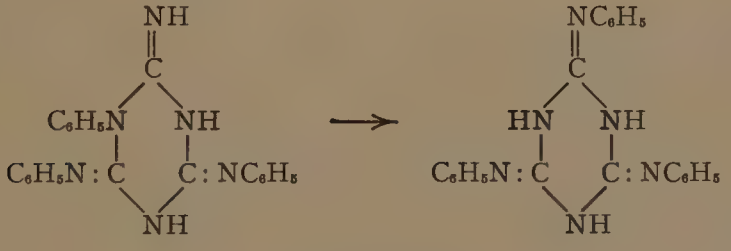
Methoxykynurine *N-Methylkynurine*

MIGRATIONS FROM NITROGEN TO NITROGEN

MELAMINES

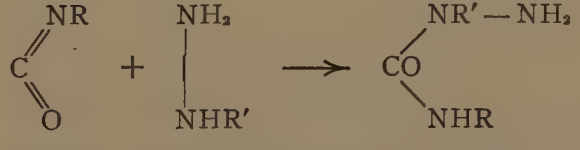
(2,4,6-triamino-s-triazines)

Rathke observed that a triphenylmelamine, in which one phenyl radical is attached to nuclear nitrogen, isomerizes when heated with hydrochloric acid.[26]



SEMICARBAZIDES

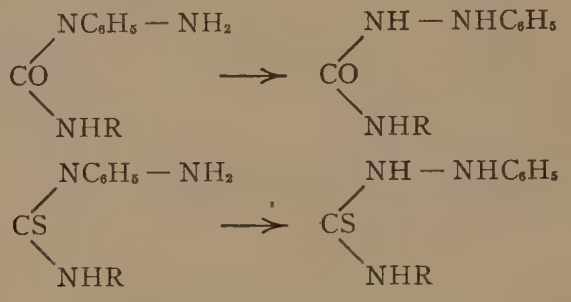
Monoalkyl hydrazines react with isocyanates, forming semicarbazides.



With isothiocyanates alkyl hydrazines form the corresponding thiosemicarbazides. These compounds are stable. Aryl hydrazines

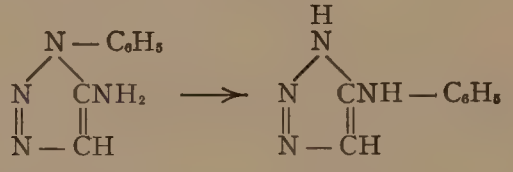
[25] Meyer, *Monatsh.*, **27**, 255 (1906).
[26] Rathke, *Ber.*, **21**, 867 (1888).

react with isocyanates and isothiocyanates in the same way but the resulting α-semicarbazides are unstable. At their melting points they isomerize to β-semicarbazides and β-thiosemicarbazides respectively.[27]

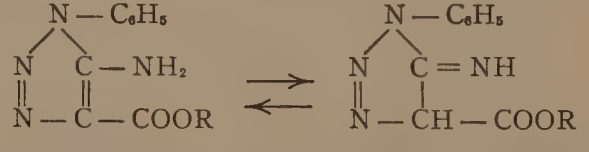


TRIAZOLES

1-Phenyl-5-amino-1,2,3-triazole is a basic crystalline compound which melts at 110° C. If held at a temperature slightly above its melting point, it changes quite rapidly into an acidic isomer melting at 139° C.



This rearrangement is said to be irreversible, but similar transpositions in some other triazole derivatives have been shown to be reversible. Thus 1-phenyl-5-amino-1,2,3-triazole-4-carboxylic ester, which fails to dissolve in bases, is converted by heat into a mixture which contains an alkali-soluble isomer. This new body can be extracted from the mixture with sodium ethylate. The resulting salt when treated with one equivalent of acid and heated in alcoholic solution in an autoclave to 150° C. is partly reconverted into the original compound. This case was at first assumed to be an example of tautomerism and was outlined as follows:[28]

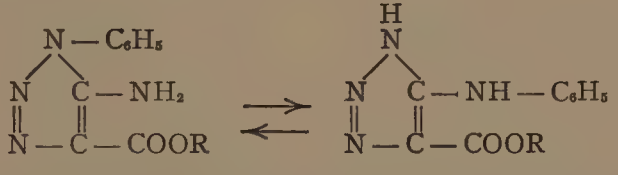


[27] Busch and Holzmann, *Ber.*, **34**, 320 (1901); Busch and Frey, *Ber.*, **36**, 1362 (1903); Busch, Opfermann and Walther, *Ber.*, **37**, 2318 (1904); Busch, *Ber.*, **42**, 4596 (1909); Busch and Reinhardt, *Ber.*, **42**, 4602 (1909). For a migration from the β to the α nitrogen see Busch and Limpach, *Ber.*, **44**, 1573 (1911).

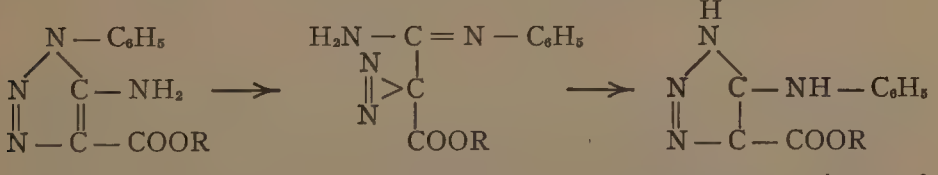
[28] Dimroth, *Ann.*, **335**, 1 (1904); **338**, 143 (1905).

No isomerism occurs, however, if the amino group attached to carbon atom number 5 be changed to NHC_6H_5. If changed to NHR in which R is not identical with the group attached to nitrogen in position 1, the rearrangement occurs. This substitution in the amino group would in no way interfere with a tautomeric shift of the remaining hydrogen atom. Or if it did interfere the tautomerism would not be reestablished by simply making the substituent in the amino group different from the nuclear substituent.

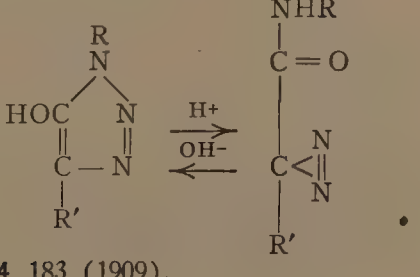
Methods for the preparation of both of the isomeric forms of this compound have been developed and the structural formulas that must be assigned to them on the basis of the synthetic procedures indicate that the above formulation of the reaction as a tautomeric shift must be abandoned in favor of the following structural change.[29]



According to Dimroth's theory the phenyl group does not migrate from the nitrogen to which it is originally attached. The break comes between nitrogen atoms 1 and 2. A new bond is then established between atom 2 and the amino nitrogen held by the carbon atom in position 5. There is a concomitant shift of hydrogen from the amino nitrogen to the one holding the phenyl radical.



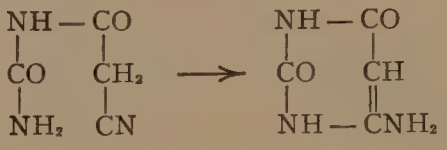
This mechanism is supported by the analogous reactions of oxytriazoles which give the corresponding diazomethane derivatives as final products.



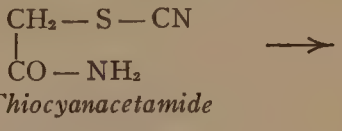
[29] Dimroth, *Ann.*, **364**, 183 (1909).

UREA DERIVATIVES

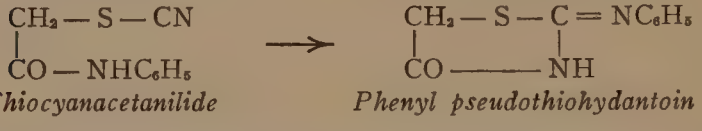
The formation of 4-aminouracil from cyanoacetylurea involves the transfer of hydrogen from one nitrogen atom to another and ring closure as a necessary consequence.[30]



The isomerization of thiocyanacetamide and its derivatives afford similar examples.[31]

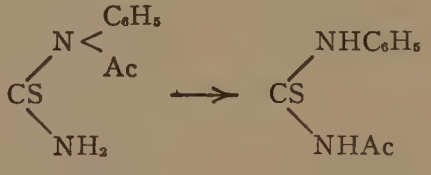


Thiocyanacetamide *Pseudothiohydantoin*

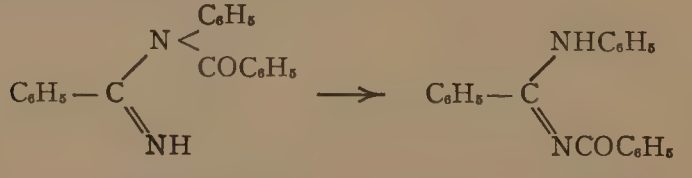


Thiocyanacetanilide *Phenyl pseudothiohydantoin*

The conversion of unsymmetrical acetylphenylthiourea into the symmetrical isomer is accomplished by heat alone.[32]



Unsymmetrical acylamidines isomerize under similar conditions. This reaction is completed within a few minutes when an alcoholic solution of the unsymmetrical benzoyl-phenyl-phenylamidine is warmed on a steam bath.[33]

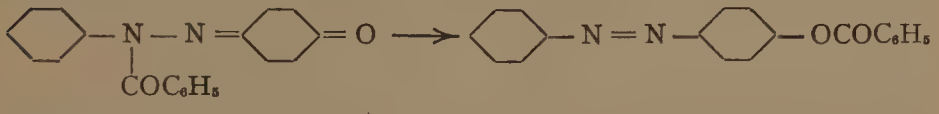


[30] Traube, *Ber.*, **33**, 3035 (1900).
[31] Miolati, *Gazz. chim. ital.*, **23**, 90 (1893); Wheeler and Johnson, *Am. Chem. J.*, **28**, 121 (1902); Johnson, *J. Am. Chem. Soc.*, **25**, 483 (1903).
[32] Wheeler, *Am. Chem. J.*, **27**, 270 (1902).
[33] Wheeler, Johnson and McFarland, *J. Am. Chem. Soc.*, **25**, 787 (1903).

MIGRATIONS FROM NITROGEN TO OXYGEN

QUINONEHYDRAZONES

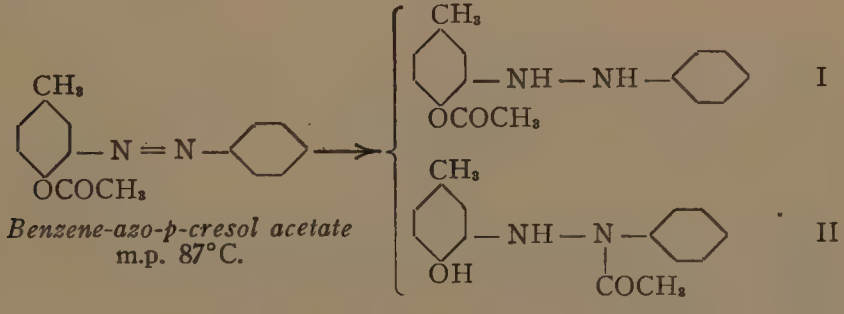
When a dry ether solution of quinonebenzoylphenylhydrazone is shaken with powdered alkali the benzoyl group migrates to the oxygen as indicated below.[34]



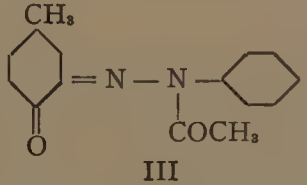
With slight modifications of the procedure, the same reaction occurs when the acetyl radical is substituted for the benzoyl group. A similar reaction occurs with β-naphthoquinonebenzoylphenylhydrazone.

An analogous transformation occurs when quinone-phenylhydrazido-formic ester is dissolved in ether and shaken with dry powdered potassium oxide.

According to Auwers benzene-azo-*p*-cresol acetate yields two reductions products.[35]



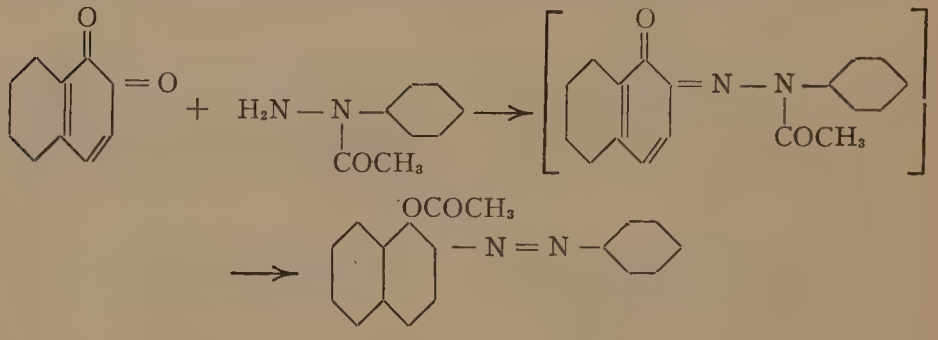
Gentle oxidation (by ferric chloride in ether suspension) should convert compound II into one of the structure



III

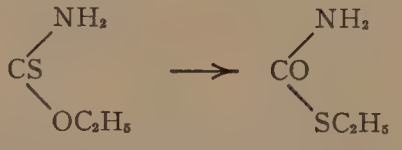
[34] Willstätter and Veraguth, *Ber.*, **40**, 1432 (1907).
[35] Auwers, *Ber.*, **40**, 2154 (1907).

This, however, does not appear as an oxidation product of the hydrazone. Instead of this the original ester melting at 87° C. is formed. In a further attempt to obtain a quinoid N-acetyl derivative of the type represented by formula III, β-phenyl-β-acetylhydrazine was condensed with α-naphthoquinone. The bracketed structure, which must have been the first product formed, could not be isolated. Here again the O-ester was the final product.

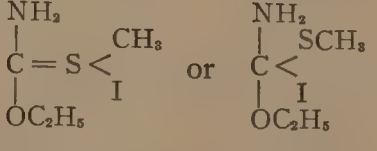


MIGRATIONS FROM OXYGEN TO SULFUR

Thioncarbamates isomerize to thiol derivatives when warmed with alkyl halides.[36]



It is highly probable that an addition product is formed as an intermediate, for mixed products are formed when one alkyl group is present in the thioncarbamate and a different alkyl radical is present in the halide which constitutes the so-called catalyst. Addition of methyl iodide to ethyl thioncarbamate might yield

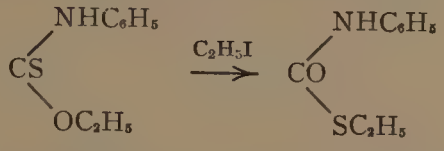


Loss of ethyl iodide from either of these would result in the formation of $NH_2—CO—SCH_3$. The liberated ethyl iodide, reacting with some of the original compound, would form an addition product which would give rise to $NH_2—CO—SC_2H_5$. This ac-

[36] Wheeler and Barnes, *Am. Chem. Jour.*, **22**, 143 (1899); Knorr, *Ber.*, **50**, 767 (1917).

counts for the appearance of the mixed products actually obtained.

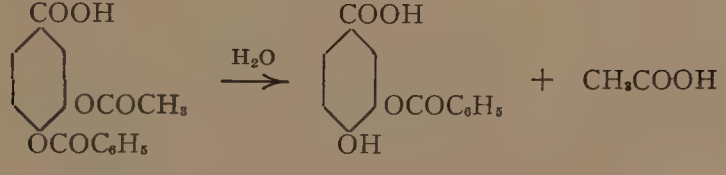
Thioncarbanilates yield thiolcarbanilates under the same treatment.[37]



MIGRATIONS FROM OXYGEN TO OXYGEN

PROTOCATECHUIC ACID

The diacetyl derivative of protocatechuic acid (3,4-dihydroxybenzoic acid) is made by warming the acid with acetic anhydride and zinc chloride. It can be half hydrolyzed by cold potassium carbonate solution. The group which resists hydrolysis in this treatment is in position 3, i.e. *meta* to the carboxyl group. Treatment with benzoyl chloride and pyridine in chloroform converts this product into 3-acetyl-4-benzoyl protocatechuic acid. When 3-acetyl-4-benzoyl protocatechuic acid is heated on a water bath in a mixture of equal volumes of acetic acid and 5 *N* hydrochloric acid, it is converted into 3-benzoyl-protocatechuic acid. The reaction is completed within thirty minutes and it is almost quantitative.[38]

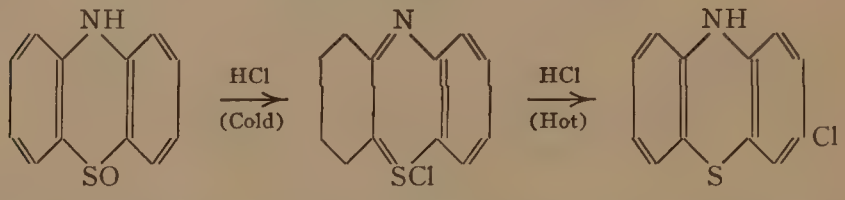


Esters of gallic acid behave in the same way. In partial hydrolysis of a triacyl derivative the two *meta* positions escape attack, and 3,5-diacetyl gallic acid when benzoylated and then partially hydrolyzed yields 3-acetyl-5-benzoyl gallic acid. The position of the hydroxyl group which was reestablished in the partial hydrolysis of the triacyl derivative was determined by converting the hydroxyl into a methoxy group through the agency of diazomethane. Complete hydrolysis then left *para*-methoxy gallic acid which was identified by its physical properties and by an independent synthesis.

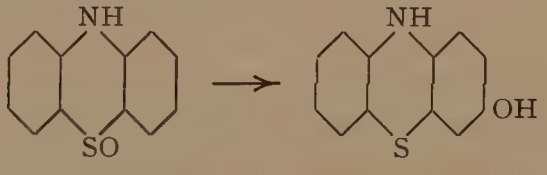
[37] Wheeler and Barnes, *Am. Chem. Jour.*, **24**, 60 (1900).
[38] Fischer, Bergmann and Lipschitz, *Ber.*, **51**, 45 (1918).

MIGRATIONS FROM SULFUR TO CARBON

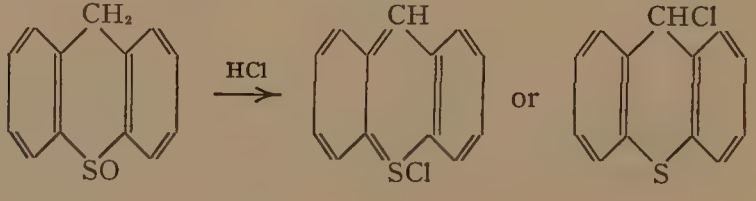
The *ortho*-sulfoxide of diphenylamine is converted by cold hydrochloric acid into phenazothionium chloride and by hot hydrochloric acid into chlorothiodiphenyl amine.[39]



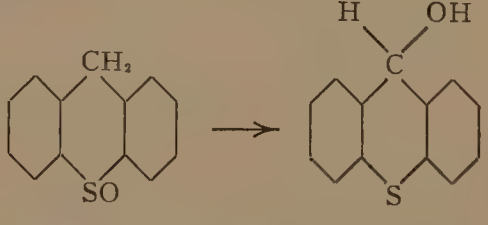
If the amine sulfoxide is heated with a weaker acid, as, for example, acetic acid, the corresponding salt fails to appear unless substituents present have increased the basicity of the sulfonium group. A hydroxy-thiodiphenyl amine is the usual final product.



Under similar treatment the *ortho*-sulfoxides of diphenylmethane yield carbothionium salts.



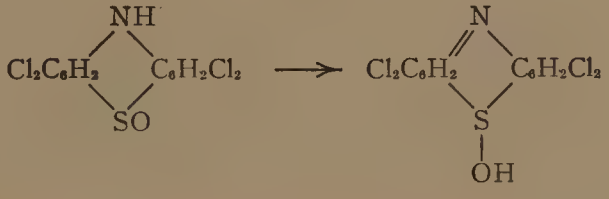
If in this case acetic acid instead of hydrochloric acid is used thioxanthenol is formed.



The appearance of thioxanthyl hydroxide in this reaction led to a search for the corresponding oximino-compound as a diphenyl-

[39] DeB. Barnett and Smiles, *J. Chem. Soc.*, **97**, 186 (1910); Brady and Smiles, *ibid.*, **97**, 1559 (1910); Page and Smiles, *ibid.*, **97**, 1112 (1910); Hilditch and Smiles, *ibid.*, **99**, 145 (1911); **101**, 2294 (1912).

amine sulfoxide derivative. It was thought that such a compound might be an intermediate in the rearrangement of an aminesulfoxide, the last step being the migration of a hydroxyl group from nitrogen to the ring. No such product was obtained. As a last resort Hilditch and Smiles used tetrachlorothiodiphenylamine, a compound so fully substituted that migration of the hydroxyl group to the ring might be prevented. But in this case heating with acetic acid produced tetrachlorophenazothionium hydroxide as a final product. The hydroxyl group did not appear on the nitrogen atom.



Chapter VI

Metatheses Involving Rearrangements

ACTION OF NITROUS ACID ON PRIMARY AMINES

In the decomposition of many primary aliphatic amines by nitrous acid the hydroxyl group fails to take the position previously occupied by the amino group. The tendency is to produce secondary and tertiary alcohols. This disposition is enhanced by the accumulation of methyl groups in the molecule as shown by the following quantitative data.[1]

1. $CH_3-CH_2-CH_2-NH_2$ →
   - $CH_3-CH_2-CH_2-OH$ (42%)
   - $CH_3-\underset{\displaystyle OH}{\overset{\displaystyle H}{\underset{|}{\overset{|}{C}}}}-CH_3$ (58%)

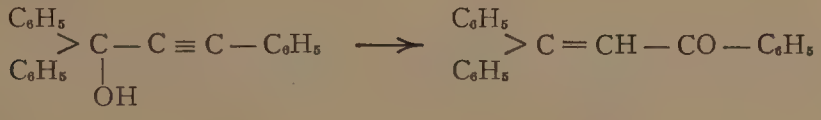
2. $H-C(CH_3)_2-CH_2-NH_2$ →
   - $H-C(CH_3)_2-CH_2-OH$ (25%)
   - $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\underset{|}{\overset{|}{C}}}}-CH_3$ (75%)

3. $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2-NH_2$ →
   - $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2-OH$ (None)
   - $CH_3-\underset{\displaystyle CH_2-CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-OH$ (100%)

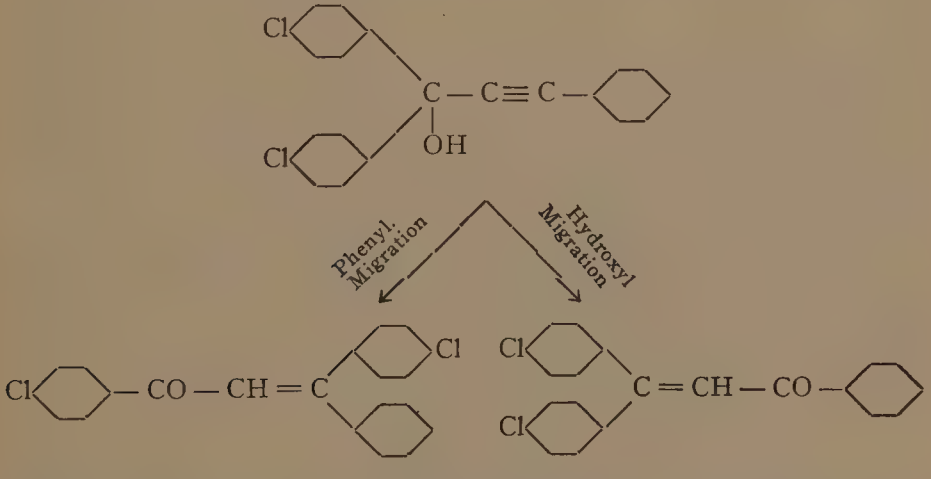
[1] Henry, *Compt. rend.*, **145**, 899, 1247 (1907); Noyes and Skinner, *J. Am. Chem. Soc.*, **39**, 2692 (1917).

MIGRATIONS IN UNSATURATED COMPOUNDS

The acetylene derivative, phenylethinyldiphenyl carbinol, prepared by Nef [2] is converted by sulfuric acid into phenylbenzalacetophenone.[3]



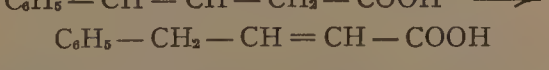
The same result is accomplished by treatment with acetic anhydride, acetyl chloride or thionyl chloride instead of sulfuric acid. The question as to whether this reaction involves the migration of a phenyl radical or of the hydroxyl group was settled by using a derivative of the above compound in which two of the phenyl groups were marked by substituents. The possible paths for the reaction are indicated below.



That the hydroxyl group shifted its position was proved by oxidizing the resulting ketone and identifying the oxidation products.

Isomerization of unsaturated acids by a shift of the double bond usually results in the establishment of the double bond in a position that effects conjugation with the carboxyl group.

Phenyl*iso*crotonic acid, when boiled with sodium hydroxide, yields the sodium salt of phenylcrotonic acid.[4]



[2] Nef, *Ann.*, **308**, 264 (1899).
[3] Meyer and Schuster, *Ber.*, **55**, 819 (1922).
[4] Hoffmann, *Ann.*, **283**, 309 (1894).

Hydrocinnamenylacrylic acid is changed in the same way to phenylpropylideneacetic acid.

$$C_6H_5-CH_2-CH=CH-CH_2-COOH \longrightarrow$$
$$C_6H_5-CH_2-CH_2-CH=CH-COOH$$

The product obtained in the hydrolysis of the cyanhydrin of cinnamic aldehyde is β-benzoylpropionic acid.[5]

$$C_6H_5-CH=CH-CHOH-CN \longrightarrow C_6H_5-CO-CH_2-CH_2-COOH$$

BROMOACETOACETIC ESTER

Bromine shifts from the α-carbon to the γ-carbon atom in bromoacetoacetic ester.[6] The α-derivative can be prepared by direct bromination of the ester. It changes slowly, but spontaneously, into the γ-modification.

$$CH_3-CO-CHBr-COOR \longrightarrow CH_2Br-CO-CH_2-COOR$$

Hantzsch suggested, as a possible mechanism, the formation of a trimethylene derivative by preliminary loss of hydrogen bromide, and re-addition of the hydrogen and bromide ions in the reverse positions. No experimental evidence supports this view. The reaction is catalyzed by hydrogen bromide and retarded by water.

A similar case is cited by Wolff,[7] who found that $\beta\beta$-dibromolevulinic acid is hydrolyzed by boiling water and that the hydrolysis product is glyoxylpropionic acid.

$$CH_3-CO-CBr_2-CH_2-COOH \longrightarrow$$
$$CHO-CO-CH_2-CH_2-COOH$$

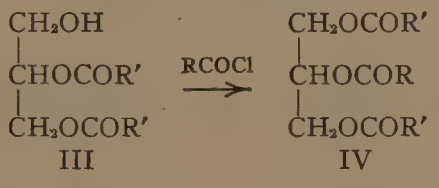
GLYCERIDES

From a monoacyl glyceride a mixed triacyl glyceride is obtained by treatment with an acid chloride containing a radical which is different from the one already in the molecule.

$$\underset{\text{I}}{\begin{matrix}CH_2OCOR\\ |\\ CHOH\\ |\\ CH_2OH\end{matrix}} \xrightarrow{2R'COCl} \underset{\text{II}}{\begin{matrix}CH_2OCOR\\ |\\ CHOCOR'\\ |\\ CH_2OCOR'\end{matrix}}$$

[5] Erlenmeyer, *Chem. Zentr.*, **1909**, II, 1998.
[6] Hantzsch, *Ber.*, **27**, 355, 3168 (1894).
[7] Wolff, *Ann.*, **260**, 79 (1890).

An α-iodide of glycerine reacts with the acid chloride R′COCl to form a diacyl-iodo-derivative from which the iodine can be removed by hydrolysis. The resulting diacyl glyceride, III, should react with the acid chloride RCOCl to yield the triacyl glyceride II. As a matter of fact an isomeric compound, IV, is produced.[8]



III IV

During the process of hydrolysis, or in the subsequent acylation, an acyl radical migrates from the β to the α position.

[8] Fischer, *Ber.*, **53**, 1621 (1920).

Chapter VII

Some Reversible Processes Commonly Classified as Rearrangements

Tautomerism is one type of a reversible rearrangement. The two or more forms of a tautomeric compound can exist together under the same conditions of temperature and pressure and in the same chemical environment. An equilibrium is established between these forms. If at equilibrium only an infinitesimal quantity of one form is present we have a case that is likely to be regarded as a rearrangement. A basic triphenylmethane dye in alkali is almost quantitatively converted into the benzoid form and it reverts almost quantitatively to the quinoid form in the presence of hydrogen ions. Either form can be isolated in the pure state. But the reversibility of the reaction removes it from the class of typical rearrangements. The subject of tautomerism is beyond the scope of this book. It is a field which is extensive enough to warrant separate treatment. There are, however, a few cases of structural modification that mark the boundaries between rearrangement, tautomerism and other types of structural variation, and some of these changes will be outlined briefly in this chapter.

MUTAROTATION

Freshly prepared solutions of many optically active compounds display rotatory powers that are not constant. The specific rotation of such a solution gradually approaches a constant value. Dextrose, when crystallized from cold water, corresponds to the formula $C_6H_{12}O_6 \cdot H_2O$. The rotatory power of a fresh aqueous solution of this compound is 110°.[1] An anhydrous form of dextrose ob-

[1] $[\alpha]_D = 110°$. $[\alpha]_D = \frac{av}{lw}$

a = observed angle of rotation (degrees).
$[\alpha]_D$ = specific rotation.
v = volume of the solution in cc.
l = length of column of solution in decimeters.
w = weight of substance in the solution (grams).

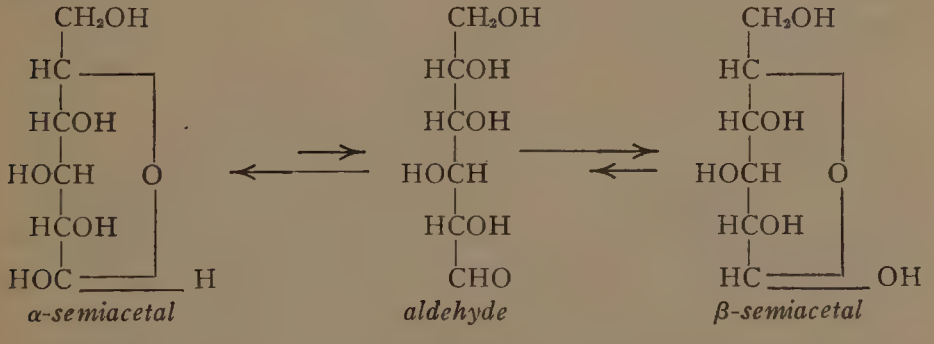
tained by crystallization from alcohol has a rotation of 19.8°. After standing for several hours an aqueous solution of either of these forms contains an equilibrium mixture of the two and has a specific rotation of 52.3°. The rate of change in rotation is in agreement with the unimolecular law.[2]

The change was at one time believed to be due to a loss or gain of water. This theory was discarded when Trey showed that the hydrated and the anhydrous forms of dextrose behave in the same way whether they are dissolved in water or in alcohol.[3]

A very early speculation relating to the possible establishment of equilibrium between two or more structural modifications has proved to be a valid explanation of the phenomenon.[4]

The γ-hydroxyacids and ϑ-hydroxyacids and the lactones derived from them show mutarotation. A freshly prepared solution of a lactone decreases in rotatory power on standing. The rotation of the corresponding acid increases. The same ultimate value is attained from either side.[5]

In the case of dextrose, mutarotation may be due to a tautomeric equilibrium between an aldehyde structure and two semiacetal forms.



The attainment of equilibrium between the optically active forms is catalyzed by hydroxide ions. Acetal formation is catalyzed by hydrogen ions. On this account some chemists consider

[2] $\frac{dx}{dt} = k(a - x)$

[3] Trey, *Z. physik. Chem.*, **18**, 193 (1895).

[4] Erdmann, *Ber.*, **13**, 2180 (1880); Dubrunfaut, *Compt. rend.*, **42**, 739 (1856); Béchamp, *ibid.*, **42**, 896 (1856); Tanret, *ibid.*, **120**, 1060 (1895); *Z. physik. Chem.*, **53**, 692 (1905).

[5] Hudson, *Z. physik. Chem.*, **44**, 487 (1903).

it unlikely that the aldehyde structure is an intermediate between the two semiacetals.

Tautomerism is responsible for mutarotation in β-ketonic acids.[6] Phenylazoacetoacetic ester changes in rotation for some time after a solution of it has been prepared.

$$CH_3-CO-\underset{\displaystyle N_2C_6H_5}{\underset{|}{CH}}-COOR \rightleftharpoons CH_3-COH=\underset{\displaystyle N_2C_6H_5}{\underset{|}{C}}-COOR$$

But when bromine is substituted for hydrogen on the α-carbon atom only one form of the compound can exist, and no change in optical activity occurs.

RACEMIZATION

An optically active form of an asymmetric compound can be converted into a racemic mixture by the application of heat. The change is catalyzed by many reagents, some of which are more or less specific for particular cases. The racemization of *d*-tartaric acid is catalyzed by aluminum tartrate.

The assumption that certain atoms or groups split off from the asymmetric carbon atom and then reattach themselves to the same atom but in reverse positions lacks experimental support. The secondary products which, according to this plan, would have a temporary existence have not been detected.

Werner has offered an explanation which avoids the necessity of severing any of the bonds in the molecule. The asymmetric carbon atom is represented as a sphere with four different atoms held by valence forces on its surface. These attached atoms or groups are in vibratory motion, the frequencies and amplitudes being determined by the temperature, by the solvent, and by the reagents present. The character of this motion and the mode of reversing the structure was represented by Werner by models as shown in Figure 3. The four different atoms, *a, b, c,* and *d,* are on the surface of a spherical central atom. Two wire loops or circular discs fastened at right angles to each other on a common axis serve to keep the balls, representing attached atoms, at proper distances from each other and from the center of the system. In Figure 3*a,* the balls are at the points of an imaginary tetrahedron. Ordinarily the vibrations of the atoms will not carry them

[6] Lapworth and Hann, *J. Chem. Soc.,* **81,** 1491 (1902).

out of the quadrants in which they are originally stationed. But in a racemizing environment, they may move far enough to attain the positions indicated in Figure 3*b*. Here the four lie in the same plane and there are equal chances for a return to their original places and for passage to the opposite hemispheres. In

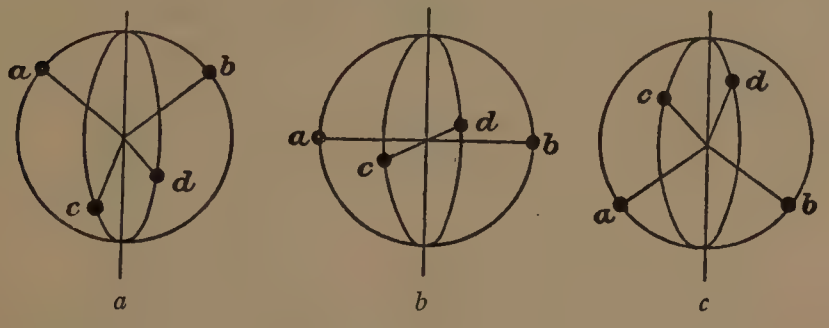
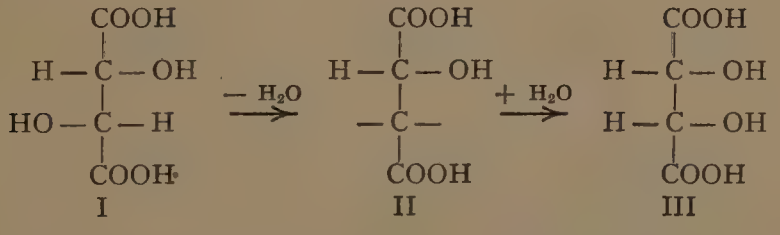


FIG. 3.

the latter case, the configuration represented by Figure 3*c* is produced and this is a mirror image of 3*a*.

Nef believed that racemization was accomplished by loss of a compound formed from two of the atoms or groups attached to the asymmetric atom and subsequent addition of the same compound.[7] Thus tartaric acid was supposed to form a bivalent radical (a methylene derivative) and water.

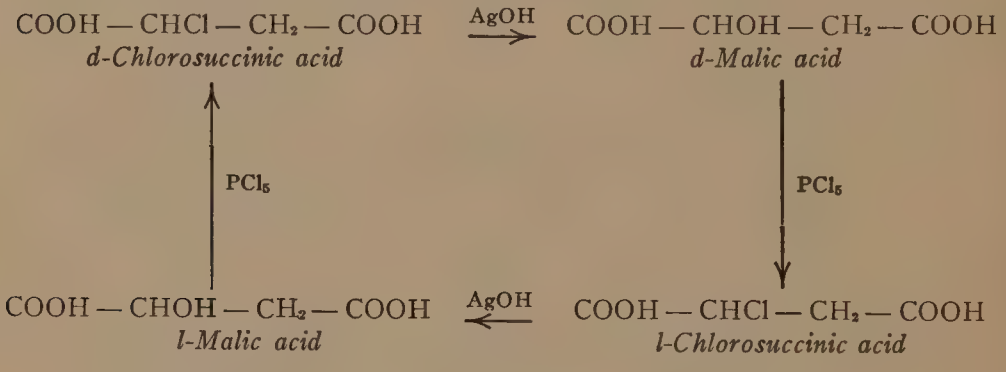


In the addition of water to II there would be equal chances for forming I and III. A similar process in connection with the second asymmetric carbon atom in mesotartaric acid, III, would yield the mirror image of I. There is, however, no substantial support for Nef's theory of methylene dissociation.

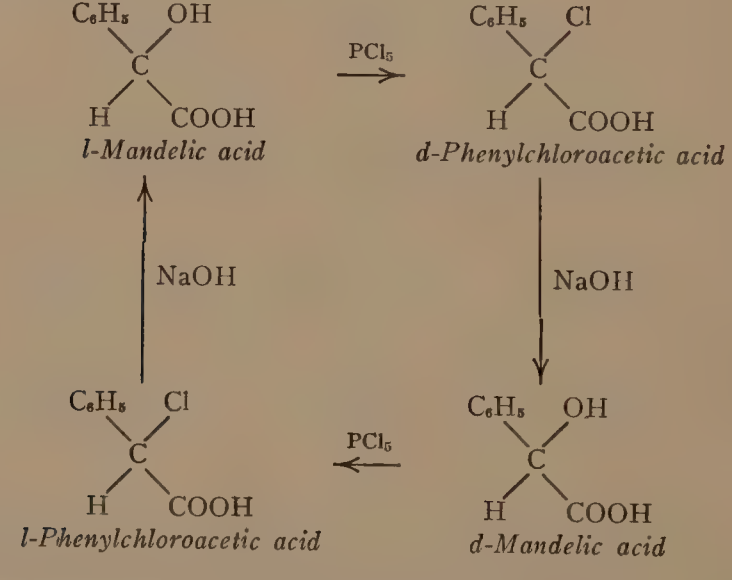
[7] Nef, *Ann.*, **335**, 191 (1904).

THE WALDEN INVERSION

Silver hydroxide converts *dextro*-chlorosuccinic acid into *dextro*-malic acid. Phosphorus pentachloride acts upon the latter, forming *laevo*-chlorosuccinic acid. The reverse of this process (conversion of the *laevo* into the *dextro* form) is likewise possible.



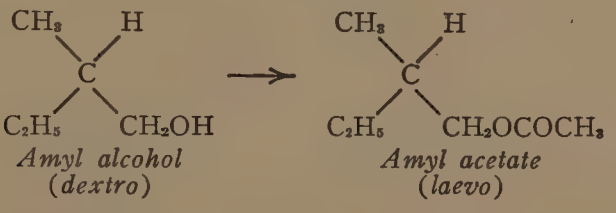
In a similar way the *dextro* and *laevo* forms of mandelic acid may be obtained.[8]



Complete cycles of this type can be established with many α-halogen and α-hydroxy acids. One of the two reagents used in a series of this kind causes a change in the stereochemical configuration of the molecule. In the examples cited, either the hydroxyl group fails to take the position vacated by chlorine in

[8] McKenzie and Clough, *J. Chem. Soc.*, **95**, 777 (1909).

one step or else, in the next phase of the cycle, chlorine fails to take the place previously occupied by the hydroxyl group.[9] The fact that the sign of the optical rotation changes as a result of a given reaction does not imply that the change in positions of the groups around the asymmetric carbon atom occurs also in this step, for there is no reason to assume that hydroxy-compounds and chloro-compounds of like structure should have similar optical properties. That a change in sign may be produced without altering the relative positions of groups attached to an asymmetric carbon atom, but merely by making a change in the composition of one of them, is proved by the fact that *dextro*-rotatory amyl alcohol yields a *laevo*-rotatory ester:

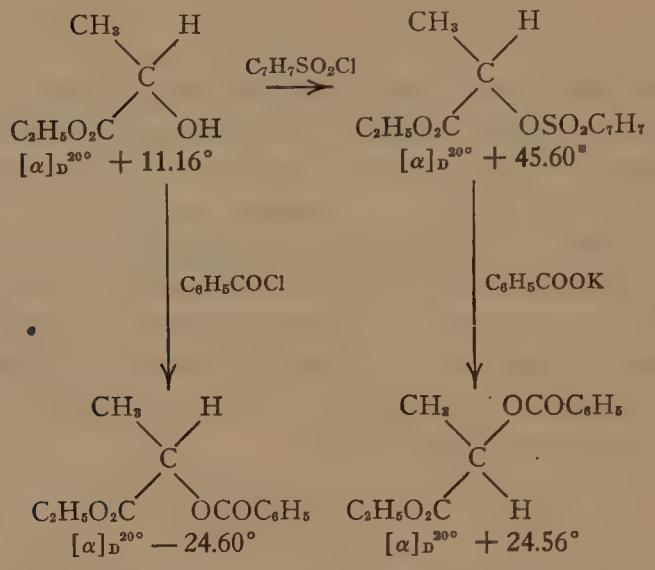


Amyl alcohol (*dextro*) → *Amyl acetate* (*laevo*)

Since at least two reactions are required to change a compound to its optical enantiomorph, it is difficult to decide which reaction actually produces the structural modification. A few cases have been reported in which it is possible to specify the stage at which inversion occurs. Ethyl-*d*-lactate may be converted into a benzoyl derivative by two paths. One procedure leads to the formation of the *dextro* derivative and the other to the *laevo* isomer.[10] Inversion accompanies the reaction with potassium benzoate which involves a valence bond of the asymmetric carbon atom.

[9] Among the more important contributions to the literature relating to the Walden inversion are the following papers: Walden, *Ber.*, **26**, 210 (1893); **28**, 1287 (1895); **29**, 133 (1896); Walden and Lutz, *Ber.*, **30**, 2795 (1897); Walden, *Ber.*, **30**, 3146 (1897); **32**, 1833, 1855 (1899); Fischer, *Ber.*, **39**, 2893 (1906); Fischer and Carl, *Ber.*, **39**, 3996 (1906); Fischer, *Ber.*, **40**, 489 (1907); Fischer and Raske, *Ber.*, **40**, 1051 (1907); Fischer and Scheibler, *Ber.*, **41**, 889 (1908); Fischer and Weichhold, *Ber.*, **41**, 1286 (1908); Fischer and Scheibler, *Ber.*, **41**, 2891 (1908); Fischer, Scheibler and Groh, *Ber.*, **43**, 2020 (1910); Werner, *Ber.*, **44**, 873 (1911); Scheibler and Wheeler, *Ber.*, **44**, 2684 (1911); Fischer, *Ann.*, **381**, 123 (1911); Leuchs, Giua and Brewster, *Ber.*, **45**, 1960 (1912); Holmberg, *Ber.*, **45**, 2997 (1912); Nef, *J. Am. Chem. Soc.*, **30**, 645 (1908); Noyes and Potter, *J. Am. Chem. Soc.*, **34**, 1067 (1912); F. E. Kendall and W. A. Noyes, *ibid.*, **48**, 2406 (1926).

[10] Kenyon, Phillips and Turley, *J. Chem. Soc.*, **127**, 399 (1925); Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

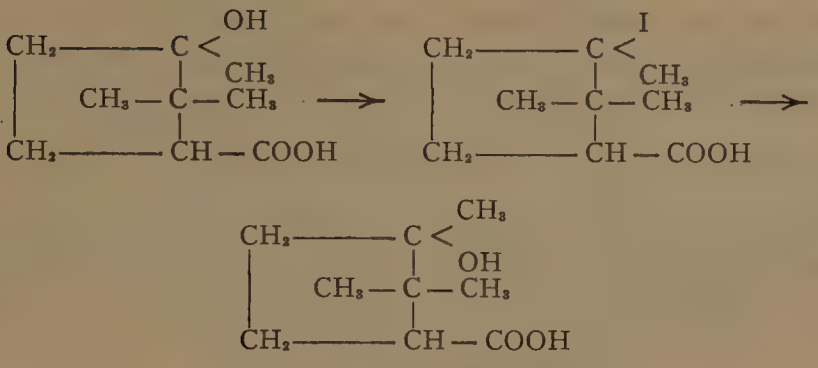


Most of the α-amino acids and some β-amino acids, like the α-halogen acids, are susceptible to the Walden inversion. Werner and Stark assume that the first step in a Walden inversion is the formation of an addition product. Potassium hydroxide, for example, acting upon bromopropionic acid, is supposed to attach itself to the asymmetric atom, through residual valence, at some place between the four groups satisfying the primary valences of the carbon. Potassium bromide is then eliminated. At the moment when the halogen is released from the carbon atom, there are two possibilities: (1) the hydroxyl group may take the place of the bromine, or (2) it may retain its intermediate position, causing the three remaining groups to shift into new positions to reëstablish the tetrahedral symmetry of the molecule.

If all molecules behave according to (1), there is no inversion. If all react as indicated in (2), there is total inversion. If half of the molecules react as in (1) and half as in (2), a racemic mixture is produced. Partial racemization always occurs in these reactions, so that any explanation of inversion must present two possible mechanisms.[11]

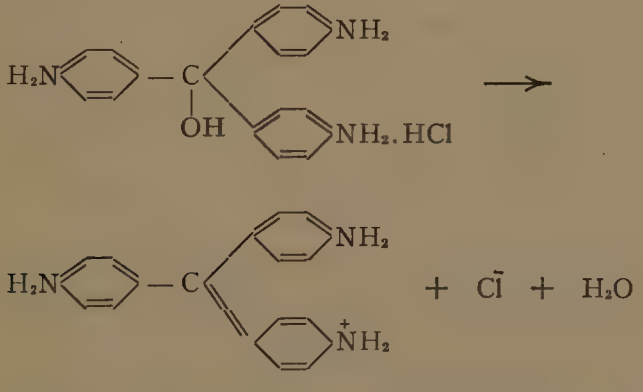
Hydrogen iodide reacts with the *cis* or the *trans* form of hydroxydihydrocampholytic acid, forming *trans*-iododihydrocampholytic acid. In one case a Walden inversion occurs.[12]

[11] Porter, "The Carbon Compounds," New York, Ginn & Co., **1926**, p. 453.
[12] Noyes and Potter, *J. Am. Chem. Soc.*, **34**, 1067 (1912).



TRIPHENYLMETHANE DYES

Aminotriphenylcarbinols are colorless compounds. They combine with acids, forming salts which spontaneously lose water and develop color. The salt formation is instantaneous. The development of color is due to a rearrangement and the time required for the change can be regulated by control of the hydrogen ion concentration.[13] Using the hydrochloride of *para*rosaniline color base as an example, the formation of a dye from a carbinol is represented by the equation

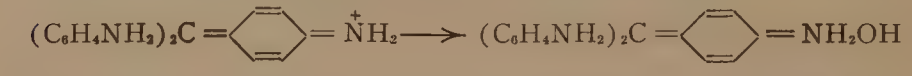


This reaction is reversible. The colored (quinoid) form takes up a molecule of water and reverts to the colorless (benzoid) form in the presence of hydroxide ions. The conversion is almost quantitative in either direction. The carbinol or color base is insoluble in water and it is precipitated completely by alkalies. On the other hand, it is dissolved completely by acids.

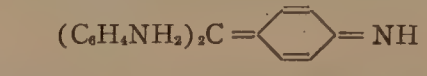
By treating *para*rosaniline with an excess of alkali Homolka obtained an imido base which is characterized by its solubility in

[13] Biddle and Porter, *J. Am. Chem. Soc.*, 37, 1571 (1915).

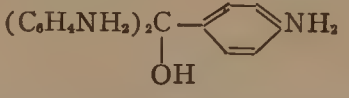
water and a distinctly alkaline reaction.[14] Hantzsch explains this by assuming that the first result of treating a triphenylmethane dye with alkali is the formation of a true nitrogen base.



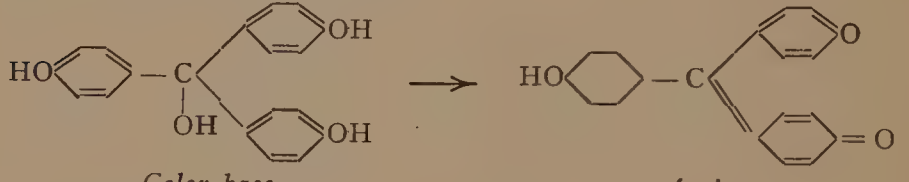
This nitrogen base may then slowly rearrange to a carbinol (color base) or, in the presence of an excess of alkali, it may immediately lose a molecule of water, forming the Homolka base.



The imido base takes up water slowly and passes into the ordinary colorless carbinol.

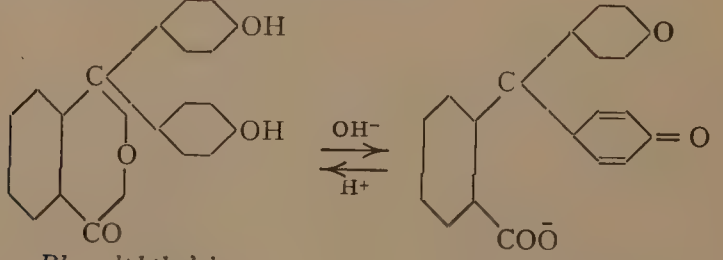


The acidic triphenylmethane dyes (those having hydroxyl groups instead of amino groups in the nuclei) are colored in alkaline solutions and colorless in the presence of acids. The transformation is represented as follows:



Color base of aurine — *Aurine*

The phthaleins constitute a division of the acidic triphenylmethane dyes and the relationship between the colorless and colored forms may be represented as follows:[15]

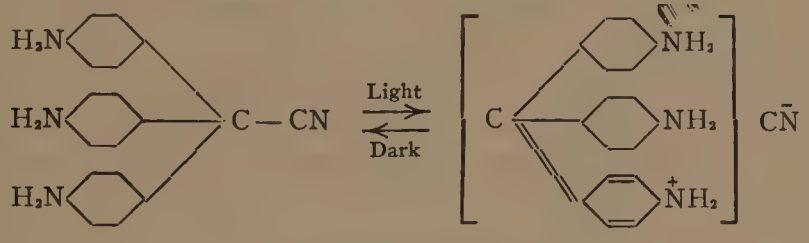


Phenolphthalein (Colorless) — *Phenolphthalein* (Red)

[14] Hantzsch, *Ber.*, **33**, 752 (1900); **37**, 3434 (1904).

[15] For a somewhat different point of view see Acree, *Am. Chem. J.*, **39**, 528 (1908).

Photochemical rearrangements of the color bases and of cyanides derived from the triphenylmethane dyes have been reported by Lifschitz and Joffe.[16] Triaminotriphenylacetonitrile dissolves in alcohol without the production of color and the colorless solution does not conduct a current of electricity. After exposure to ultraviolet radiation for several hours the solution acquires a color and becomes an electrolyte. The color disappears in the course of a few weeks if the solution is kept in the dark.



ALKYL BROMIDES

Under the catalytic influence of an aluminum salt *normal*-propyl bromide is converted into *iso*propyl bromide. The reaction is slow at ordinary temperatures but rapid at the boiling point of the primary compound.[17] Pure *normal*-propyl bromide can be distilled without appreciable decomposition if no catalyst is present. Although complete conversion has been reported, it is probable that an equilibrium actually exists between the two forms.

An equilibrium is established between *iso*butyl bromide and *tertiary*butyl bromide.

$$(CH_3)_2CH-CH_2Br \rightleftharpoons (CH_3)_3CBr$$

When either compound is heated in a sealed tube to 260° C. for several hours a mixture is produced.[18] Different investigators have reported values ranging between 75% and 94% for the quantity of *tertiary*butyl bromide present when equilibrium is established at 260° C. The reaction is said to proceed through the dissociation of the alkyl halide into hydrogen bromide and *iso*butylene. These products then recombine to form either the original or the isomeric compound.[19] The relative rates of dissociation and of the two

[16] J. Lifschitz and C. L. Joffe, *Zeit. physik. Chem.*, **97**, 426 (1921).
[17] Gustavson, *J. Russ. Phys-Chem. Soc.*, **1**, 61 (1883); Gustavson, *Ber.*, **16**, 958 (1883).
[18] Brunel, *Ber.*, **44**, 1000 (1911).
[19] Eltekoff, *Ber.*, **8**, 1244 (1875); Iwworsky, *Ann.*, **354**, 325 (1907).

possible modes of recombination determine the condition of equilibrium. This view of the mechanism has been opposed on the ground that the rearrangement occurs readily at comparatively low temperatures and there is no direct evidence of the production of hydrogen bromide under such conditions.[20] Michael and Leupold believe the reaction does not depend upon a dissociation but is due to a direct interchange between hydrogen and bromine within a single molecule. They found no evidence of dissociation at low temperatures. The dissociation of an alkyl bromide is catalyzed by a great variety of substances [21] and the presence of one of these may account for the success of the rearrangements that some investigators have observed at lower temperatures. By means of vapor pressure measurements Brunel was able to detect dissociation in nearly all of his experiments at temperatures ranging from 100° C. to 275° C. He measured the rates of approach to constant pressures when each of the pure bromides was heated to definite temperatures. He analyzed the mixtures produced by these treatments and obtained similar results by heating equimolal mixtures of pure *iso*butylene and hydrogen bromide.[22]

In an application of the Friedel and Crafts' reaction *iso*butyl bromide was dissolved in benzene and treated with aluminum chloride (cold) for two days. The product obtained was *tertiary*-butyl benzene.[23]

Alcohols of the type $RCOH{=}CH{-}CH_3$ isomerize to $RCH{=}CH{-}CH_2OH$ [24] or to $R{-}CO{-}CH_2{-}CH_3$.

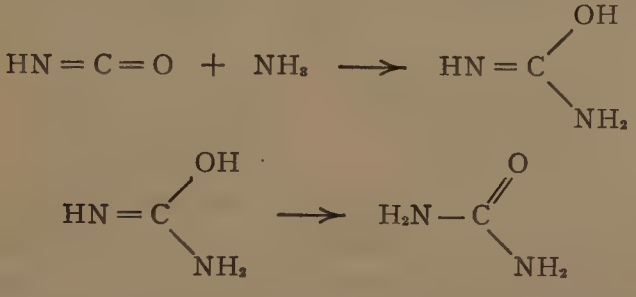
AMMONIUM CYANATE AND UREA

Wöhler's classical experiment with ammonium cyanate represents the first observed case of a molecular rearrangement as well as the first synthesis of an organic compound from inorganic sources.[25] The reaction has been proved to be reversible.[26]

[20] Michael and Leupold, *Ann.*, **379**, 263 (1911).
[21] Menschutkin and Konowalow, *Ber.*, **17**, 1361 (1884); Konowalow, *Ber.*, **18**, 2808 (1885).
[22] Brunel, *Ann.*, **384**, 245 (1911).
[23] Schramm, *Monatsh.*, **9**, 613 (1889). Reviewed in *Ber.*, **21**, 782 (1888). (Patent Section.)
[24] Prevost, *Compt. rend.*, **185**, 1283 (1927).
[25] Wöhler, *Ann.* (Pogg.), **12**, 253 (1828); Liebig and Wöhler, *Ann.* (Pogg.), **20**, 393 (1830).
[26] Walker and Hambly, *J. Chem. Soc.*, **67**, 746 (1895); Walker, *J. Chem. Soc.*, **71**, 489 (1897); Escales, *Chem. Zeit.*, **35**, 595 (1911).

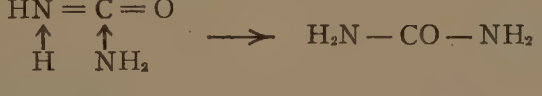
Walker and Hambly measured the rate of this transformation at temperatures ranging from 22° C. to 100° C. At 100° C. equilibrium is attained within 120 hours. The mixture at that point is 97% urea.

Walker assumes that the salt dissociates into ammonium and cyanate ions and that these ions recombine in such a way as to produce urea. Chattaway, on the other hand, believes it is due to a dissociation into ammonia and cyanic acid followed by addition in the same way that ammonia adds to any carbonyl group.[27]

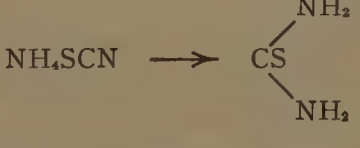


The formation of substituted ureas by addition of ammonia or amines to isocyanic esters are cited as reactions of the same type.

Wheeler accepts Chattaway's view with reference to the dissociation of ammonium cyanate but believes the addition of ammonia to cyanic acid does not involve the intermediate enol.[28] He represents the reaction as follows:

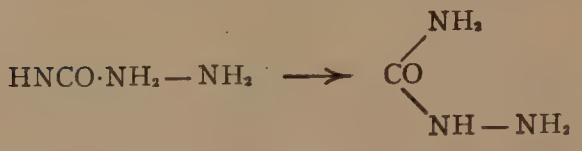


Ammonium thiocyanate, when heated, yields thiourea.

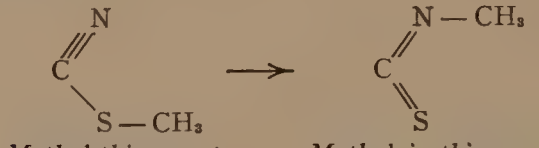


Under the same treatment hydrazine cyanate is converted into semicarbazide.

[27] Chattaway, *J. Chem. Soc.*, **101**, 170 (1912).
[28] Wheeler, *J. Am. Chem. Soc.*, **34**, 1269 (1912).



The transformation of a thiocyanate into an *iso*thiocyanate is a similar reaction.[29] As an example the case of methyl thiocyanate may be cited. The compound is prepared by distilling a mixture of potassium sulfocyanate and methyl potassium sulfate. It is stable at 100° C., but when heated in a sealed tube to 180° C. for five or six hours two products are formed. One is a crystalline polymer of methylthiocyanate and the other is methyl*iso*thiocyanate or methyl mustard oil.[30]



Methyl thiocyanate (b.p. 132°C.) *Methyl isothiocyanate* (b.p. 119°C.)

This change occurs more readily with allyl thiocyanate. The process is rapid and nearly quantitative at its boiling point, 161° C. The product, allyl *iso*thiocyanate (b.p. 150.7° C.), is the principal component of the oil derived from mustard seeds.

SULFONIC ACIDS

In some of the aromatic sulfonic acids the SO_3H group migrates when the compound is heated with sulfuric acid. In this way naphthalene-2-7-disulfonic acid is converted into naphthalene-2-6-disulfonic acid.

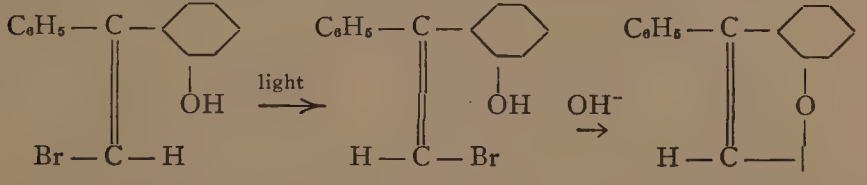
There are conflicting statements with reference to the extent of this reaction. Erbert and Merz reported complete conversion at 180° C. within twenty-four hours.[31] Fierz-David and Hasler claim that equilibrium is established before half of the 2-7-disulfonic

[29] Johnson and Levy, *Am. Chem. J.*, **38**, 456 (1907); Johnson and Storey, *Am. Chem. J.*, **40**, 131 (1908).
[30] Hofmann, *Ber.*, **13**, 1350 (1880).
[31] Erbert and Merz, *Ber.*, **9**, 592 (1876).

acid has been changed.[32] Heid finally established the fact of reversibility.[33] The failure to obtain concordant results is probably due to side reactions being highly susceptible to catalytic influences, and different men have not worked under identical conditions. The same investigator finds different compositions at equilibrium when one experiment is conducted in glass apparatus and another in iron.

ETHYLENE DERIVATIVES

There have been numerous photochemical conversions of ethylene derivatives into stereoisomeric forms.[34] Of the two *ortho*-hydroxyphenylbromoethylenes the member which melts at the higher temperature is incapable of ring formation. The lower melting form, on treatment with alkali, yields β-phenylcumarone. The former can be converted into the cumarone by the following path.



The stable *trans*-dibenzoylethylene has been changed quantitatively into the labile *cis*-dibenzoylethylene by light [35] and a partial conversion of maleic acid into fumaric acid has been accomplished in the same fashion with and without the aid of catalysts.[36]

Either form of *ortho*-anisylcinnamic acid is converted into an equi-molal mixture of the *cis* and *trans* isomers by an exposure of 160 to 200 hours to a quartz mercury vapor lamp.[37]

The formation of a labile compound from a stable isomer indicates an increase in the energy content of the system. Stoermer accounts for this phenomenon as a result of absorption of radiant

[32] Fierz-David and Hasler, *Helv. chim. Acta.*, **6**, 1133 (1923).
[33] Heid, *J. Am. Chem. Soc.*, **49**, 844 (1927).
[34] Stoermer and Simon, *Ber.*, **37**, 4163 (1904).
[35] Paal and Schulze, *Ber.*, **35**, 168 (1902).
[36] Ciamician and Silber, *Ber.*, **36**, 4266 (1903); Bruner and Krolikowski, *Chem. Zentr.*, **1910**, II, 1881; Meerwein and Weber, *Ber.*, **58**, 1266 (1925).
[37] Stoermer, Ber., **42**, 4865 (1909).

energy and points out that the reverse process (change from labile to stable form) is better known merely because most of these rearrangements have been studied under conditions that favored a loss of energy.

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